INCIDENCE AND RISK FACTORS FOR RESIDUAL NEUROMUSCULAR BLOCKADE IN POST ANAESTHESIA CARE UNIT AMONG PATIENTS RECEIVING INTERMEDIATE ACTING NEUROMUSCULAR BLOCKING DRUGS

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF M.D BRANCH –X (ANAESTHESIOLOGY) EXAMINATION OF THE TAMILNADU DR.MGR MEDICAL UNIVERSITY TO BE HELD IN APRIL 2016

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Dr Raj Sahajanandan

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Professor and Head of Unit - 4

Department of Anaesthesiology

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CERTIFICATE

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Dr Davis Cherian

Postgraduate Registrar

Registration Number:

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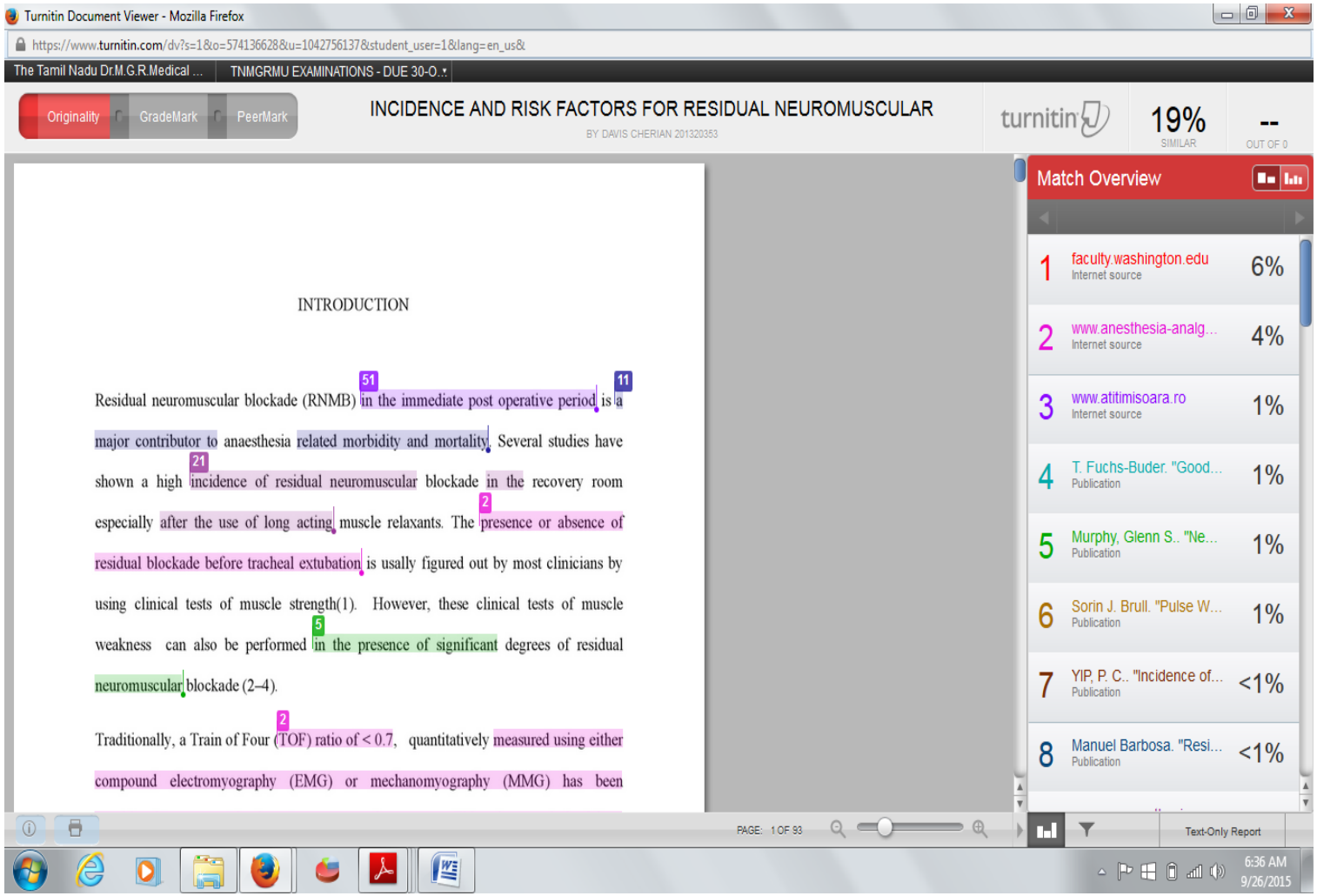
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INTRODUCTION
Residual neuromuscular blockade (RNMB) in the immediate post operative period is a major contributor to anaesthesia related morbidity and mortality. Several studies have shown a high incidence of residual neuromuscular blockade in the recovery room especially after the use of long acting muscle relaxants. The presence or absence of residual blockade before tracheal extubation is usally figured out by most clinicians by using clinical tests of muscle strength(1). However, these clinical tests of muscle weakness can also be performed in the presence of significant degrees of residual neuromuscular blockade (2–4).
Traditionally, a Train of Four (TOF) ratio of < 0.7, quantitatively measured using either compound electromyography (EMG) or mechanomyography (MMG) has been
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September 22, 2014

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Sub: **Fluid Research Grant:**
Incidence and risk factors for residual neuromuscular blockade in the post anesthesiacare unit among patients receiving intermediate acting neuromuscular blocking drugs.
Dr. Davis Cherian, PG Registrar, Dr. Raj Sahajanandan, Dr. Justin James, Anaesthesiology, CMC, Vellore

Ref: IRB Min Nos 8940 [OBSERVE] dated 07.07.2014

Dear Dr. Davis Cherian,

I enclose the following documents:

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
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Ref: IRB Min Nos 8940 [OBS:R:V2] dated 07.07.2014

Dear Dr. Davis Cherian,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Incidence and risk factors for residual neuromuscular blockade in the post anesthesiacare unit among patients receiving intermediate acting neuromuscular blocking drugs." on June 07th 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Davis Cherian, Raj Sahajanandan, Justin James.
3. Proforma
4. Informed Consent form (English & Tamil)
5. Information sheet(English & Tamil)
6. No of documents 1-5

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on June 07th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB-Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/ratio/research/index.html

Fund Grant Allocation:

A sum of 75,000/- INR (Rupees Seventy Five Thousand only) will be granted for 18 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
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Cc: Dr. Raj Sahajanandan, Anaesthesiology, CMC, Vellore

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I am thankful to Dr. Justin P James, Assistant Professor, Department of Anaesthesiology, Christian Medical College and Hospital, Vellore for his guidance and time.

I am also extremely thankful to all my friends and colleagues, from the Department of Anaesthesiology and the recovery room staff for helping me in collecting the cases and for their help in making this study a reality.

I wish to thank Mr. Bijesh from the Department of Biostatistics for patiently analyzing the data. I would like to thank the Fluid Research Committee, CMC Hospital for granting me permission for conducting this study and for the financial assistance.

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INDEX

INTRODUCTION

Residual neuromuscular blockade (RNMB) in the immediate post operative period is a major contributor to anaesthesia related morbidity and mortality. Several studies have shown a high incidence of residual neuromuscular blockade in the recovery room especially after the use of long acting muscle relaxants. The presence or absence of residual blockade before tracheal extubation is usually figured out by most clinicians by using clinical tests of muscle strength(1). However, these clinical tests of muscle weakness can also be performed in the presence of significant degrees of residual neuromuscular blockade (2–4).

Traditionally, a Train of Four (TOF) ratio of < 0.7, quantitatively measured using either compound electromyography (EMG) or mechanomyography (MMG) has been considered to represent inadequate neuromuscular recovery. This value was derived from several studies published in the 1970s. (5–7)More recent data suggested TOF ratios must recover to values > 0.9 to ensure adequate recovery which is currently taken as the gold standard(2, 8, 9).

Adverse events associated with residual NMB, that is a TOF ratio < 0.9, are prolonged postoperative recovery, respiratory dysfunction, impaired airway protective reflexes, and unpleasant symptoms of muscle weakness.(2,9,10) TOF value < 0.9, has also been associated with postoperative pulmonary complications critical respiratory events in the post-anaesthetic care unit (PACU) and delay in discharge from PACU .(11–13)

This study aims to find the current incidence of residual neuromuscular blockade in the recovery room as defined by TOF ratio < 0.9 and document the factors affecting it to identify the risk factors for residual NMB. The study also aims to observe the need for airway support, the incidence of desaturation and the delay in discharge from the PACU in patients with and without RNMB

AIM

Primary Aim

To determine the incidence of residual neuromuscular blockade in the recovery room.

Secondary Aim

To identify the risk factors of residual neuromuscular block

To determine the incidence of complications due to residual NMB

OBJECTIVES

PRIMARY:

To determine the incidence and risk factors of residual neuromuscular blockade in the recovery room among patient receiving intermediate acting neuromuscular blocking drugs

SECONDARY:

1. To determine the incidence of early adverse respiratory events in patients with residual neuromuscular blockade

2. To determine whether residual neuromuscular block is associated with delayed discharge from recovery room.

LITERATURE REVIEW

Residual neuromuscular blockade (RNMB) in the immediate post operative period is a major contributor to anaesthesia related morbidity and mortality. Most clinicians depend on clinical signs or tests of muscle weakness to detect residual blockade before tracheal extubation (1). However, these clinical tests of muscle weakness can be performed with significant degrees of residual block (2–4). To understand the problem and to avoid residual neuromuscular block we need to have an understanding of the physiology of neuromuscular junction and pharmacodynamics of neuromuscular blocking drugs.

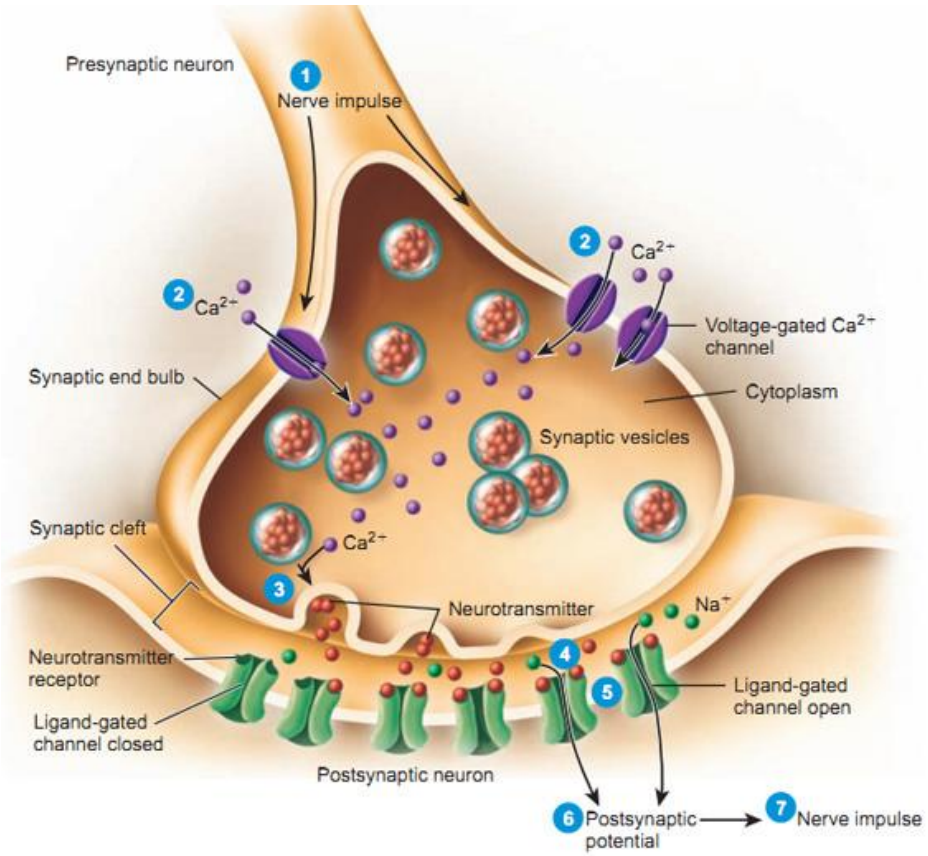
STRUCTURE OF NEUROMUSCULAR JUNCTION

The skeletal muscles are supplied by motor neurons whose cell bodies lie in the spinal cord. The information from the central nervous system is carried from the spinal cord by the axons of these motor nerves to distant parts of the body where they supply many muscle cells (or fibers) after branching into multiple nerve terminals. At the terminal portions of the axon is the synapse, a specialized structure, for the production and release of acetylcholine. A narrow gap separates the endplate of the muscle fiber and the synapse, called the synaptic cleft, which is approximately 50 nm in width (Fig 1)(14–16)

Neuromuscular blocking drugs mainly act at the nicotinic cholinergic receptor at the end plate of the muscle. They also have effects on presynaptic receptors. The acetylcholine

receptors are clustered at the end plate, especially at the crests of the folds, and in adults is almost nil at the extrajunctional areas.(14, 16)

FIGURE 1: The Neuromuscular junction



Acetylcholine release

Acetylcholine, the transmitter at the neuromuscular junction, is released from the presynaptic nerve endings when a nerve impulse (action potential) passes through the axon into the nerve terminal. It is synthesized from choline and acetate by the enzyme choline acetyltransferase and is stored in the vesicles of the terminal. These vesicles are 45 nm in size and each contains about 5000 to 10000 acetylcholine molecules. Acetylcholine is released in packets or quanta, and a quantum represents the contents of one vesicle. During an action potential, around 200 to 400 quanta are released, which amounts to around 1 to 4 million acetylcholine molecules into the synaptic cleft.

Calcium is required for the binding and fusion of vesicles and release of acetylcholine. It enters the nerve terminals through channels which open when the depolarization occurs. The release process maybe inhibited when there is reduced calcium concentration or calcium is antagonized by magnesium and transmission failure may occur.

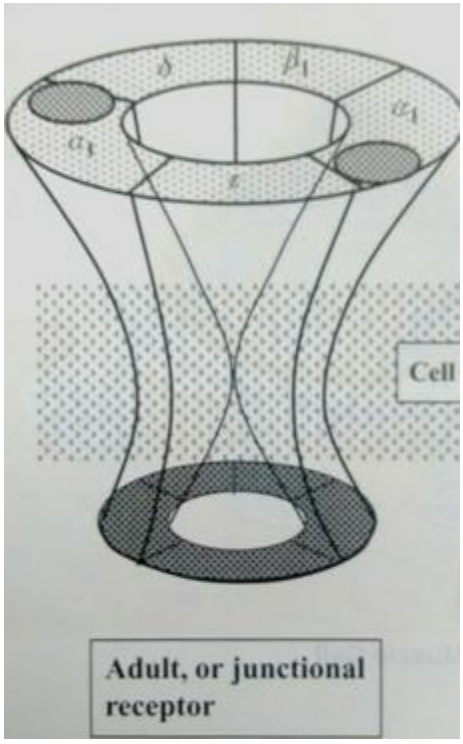
Postsynaptic changes

The muscle endplate receptors are the nicotinic cholinergic type. These receptors are made of five glycoprotein subunits arranged in the form of a rosette and lying across the cell membrane (Fig 2). The nicotinic subtype at the neuromuscular junction is made up of two identical α sub units, and three others, β, δ and ε. The 2 α sub units have acetylcholine binding sites on their outside part. When two acetylcholine molecules bind simultaneously to each binding site, an opening forms in center of the rosette, which

allows movement of cations like sodium and potassium along their concentration gradients.

The predominant change is the movement of sodium ions into the cell due to the negative voltage of the inside of the cell. This movement makes the inside of the endplate less negative, that is, it gets depolarized. There is a high density of sodium channels in the folds of the synaptic cleft and the perijunctional area which open when the membrane depolarization reaches a critical point, causing further depolarization by entry of sodium into the cell. An action potential is propagated by this depolarization, which propagates through the whole length of the muscle fiber by activation of the sodium channels.

Fig 2: The adult junctional nicotinic cholinergic receptor



The main action of non depolarizing neuromuscular blocking drugs is to bind to at least one of the two α subunits of the postsynaptic receptor. This prevents access to the receptor by acetylcholine and does not produce opening of the receptor. Normally only a small fraction of available receptors must be bound by acetylcholine to produce sufficient depolarization to initiate a muscle contraction, hence, there is a wide margin of safety (17).

The acetylcholine released is hydrolyzed rapidly by the enzyme acetylcholinesterase, which is present in the folds of the end plate, and also in the basement membrane of the synaptic cleft.

Other than the postsynaptic receptors, there are presynaptic receptors also present whose role is to mobilize the acetylcholine vesicles and to maintain the number of vesicles to be released. Non depolarizing and neuromuscular blocking drugs produce characteristic TOF and tetanic fade by probably blocking presynaptic nicotinic receptors, thus preventing mobilization of acetylcholine vesicles and leading to decreased acetylcholine release during high frequency stimulation (14,18).

WHAT ARE MUSCLE RELAXANTS?

Curare, the South American arrow poison, was among the first known paralytic agents to be used, an account of which is documented as early as 1595. (19) It was only during 1940's when d- Tubocurarine (dTc) began to be used for skeletal muscle relaxation in

surgeries.(20) (21) Other Neuromuscular blocking drugs (NMBDs) have been introduced into clinical practice since the use of dTc was first advocated. The commonly used NMBD's, Vecuronium and Atracurium were introduced into clinical practice from 1980s, whereas, Mivacurium and Rocuronium came in the 1990's.(19–22) NMBDs interrupt transmission of nerve impulses at the neuromuscular junction (NMJ) and thereby produce paresis or paralysis of skeletal muscles. They are competitive antagonists of nicotinic acetylcholine receptors at the neuromuscular junction, whose effect degrades with time after administration. They compete against the neurotransmitter acetylcholine for the nicotinic receptors on the muscle endplate. The principal uses of NMBDs in the operation theatre are to produce skeletal muscle relaxation for facilitation of instrumentation of the airway and mechanical ventilation, and to improve operating conditions.

Reversal of muscle relaxants

The effects of the neuromuscular blocking drugs can be reversed by increasing the concentration of acetylcholine at the neuromuscular junction. This is achieved by antagonizing cholinesterase enzyme which degrades acetylcholine. The commonly used anticholinesterase drugs are Neostigmine, Physostigmine and Edrophonium. Pharmacological reversal of neuromuscular block with anticholinergic drugs like Physostigmine and Neostigmine was first suggested in 1945 (23). By the 1960's, the practice of reversal of neuromuscular block was different in the United States and

Europe. In Great Britain the majority of the patients received at least some anticholinesterase drug at the end of anaesthesia whereas reversal drugs were not deemed necessary in the United States, as smaller doses of curare were used, and the emphasis was more on the mortality and morbidity associated with reversal drugs. (24)

The adverse effects known to be associated with anticholinesterase are

- Anticholinesterase associated paradoxical weakness which occurs when full doses of Neostigmine are given to patient who have recovered completely from NMBDs. Increased upper airway collapsibility, diaphragm muscle weakness and decreased genioglossus tone were also observed.(25–27)
- Nausea and vomiting, though studies done till now are inconclusive.
- Cardiovascular effects due to muscarinic receptor stimulation and pronounced vagal effects. Atropine or Glycopyrrolate is usually given to counteract these side effects.
- Bronchoconstriction also occurs due to muscarinic receptor stimulation and can be avoided if anticholinergics are used concomitantly.

The practice of reversal of neuromuscular blocking drugs still has significant differences. Osmer et al showed that, Anesthesiologists in great Britain routinely reversed the patients at the end of the procedure, as compared to their French and German counterparts(28). Surveys from Germany, in 2003, and France, in 2008, suggest that only a minority of clinicians practice routine reversal of neuromuscular blockade at the end of an anaesthetic(29,30). A survey done in 2010, among 2636 anesthesiologists working in

Europe and United States, showed that routine pharmacological reversal was less commonly practiced in Europe than in United States(31). No such surveys are available in India regarding the practice of reversal of neuromuscular blocking drugs. More than 60 years since the introduction of muscle relaxants, as indicated in the above surveys, there is little agreement about "best practices" in the use of NMBDs, their reversal drugs, or the monitoring of depth of neuromuscular blockade)

WHAT IS RESIDUAL NEUROMUSCULAR BLOCKADE?

Definition

Residual neuromuscular block is the presence of signs or symptoms of muscle weakness in the postoperative period after the intra operative administration of an NMBD.

Signs that residual paralysis is present may include inability to perform a head lift, hand grip, eye opening, or tongue protrusion; inability to clench a tongue depressor between the incisor teeth; inability to smile, swallow, speak, cough, track objects with eyes; or inability to perform a deep or vital capacity breath.(32)Symptoms of residual blockade that have been reported include subjective difficulty of performing the aforementioned tests, as well as blurry vision, diplopia, facial weakness, facial numbness, and general weakness.(32,33)

Quantitative neuromuscular monitoring has traditionally been used to define residual neuromuscular block. Peripheral nerve stimulation for neuromuscular monitoring was introduced in the early 1970s by Ali et al. The ulnar nerve adductor pollicis unit was monitored using Train of Four response (TOF) (6) Four supramaximal stimuli were delivered every 0.5 seconds (2 Hz), and the muscle responses were noted using evoked mechanomyography or electromyography . By comparing the amplitude of the fourth (T4) to the first (T1) evoked mechanical or electromyographic response (TOF ratio), the degree of neuromuscular recovery could be measured. These authors then proceeded to compare the residual weakness present in the hand (defined using quantified T4/T1 ratio, i.e., TOF ratio) with symptoms of peripheral muscle weakness and spirometry measurements.

TOF < 0.7

TOF ratio of <0.7 was initially used to define residual neuromuscular blockade. This value was derived from several studies published in the 1970's comparing the TOF ratio to various signs and symptoms of peripheral muscle weakness.(5–7) Ali et al observed that with a TOF ratio of > 0.7 with subjects were able to open eyes widely, cough, protrude the tongue, sustain head lift for 5 seconds, develop a forced vital capacity of at least 15 to 20 mL/kg, and sustain tetanic stimulation without fade for 5 seconds.(5) The same group observed in another investigation that changes in measured respiratory variables, including tidal volume, vital capacity, inspiratory force, and peak expiratory flow rate, were "negligible" until TOF ratios decreased to <0.6.(6) Similar findings were

observed by Brand et al. At a TOF ratio of 0.7, all patients were able to sustain eye opening, hand grasp, and tongue protrusion, whereas 9 of 10 were able to maintain a 5-second head lift.(7)

TOF < 0.9

Recently done studies have observed clinically significant symptoms of muscle weakness in patients having TOF ratio up to 0.9. Studies done in awake volunteers concluded that at a TOF ratio <0.9 impaired pharyngeal function, airway obstruction, an increased risk of aspiration of gastric contents, an impaired hypoxic ventilatory control and unpleasant symptoms of muscle weakness was present. (2, 8, 9, 33, 34) Based on these studies, a TOF ratio of > 0.9 (on EMG or MMG) was suggested as the new "gold standard".

Assessment of RNMB

In order to optimize patient safety, tracheal extubation in the operating room should not occur until complete recovery of muscle strength is present and the residual effects of NMBDs have been fully reversed (or spontaneously recovered). Therefore, clinicians have methods to detect and treat residual muscle weakness. The commonly used methods to determine the presence or absence of residual neuromuscular blockade in the operating room can be divided as:

- Clinical tests for signs of muscle weakness
- Qualitative neuromuscular monitors
- Quantitative neuromuscular monitors.

Clinical tests for signs of muscle weakness

An ideal clinical test should be applicable and reliable before emergence from anesthesia and tracheal extubation and not require an awake and cooperative patient. Unfortunately, one of these criteria is not met by both tests. In addition, most of the tests are not specific for the respiratory function, so they cannot infer the adequacy of respiratory muscle function clinically. Ironically, conclusion of residual weakness is surmised by most physicians based on the ability of the patients to successfully perform tests of muscle weakness (1)Furthermore, one of the primary factors that determines whether clinicians elect to administer a reversal drug at the end of surgery is the presence of signs of muscle weakness.(31)Majority of clinicians also believe that residual neuromuscular blockade can be reliably excluded just on the basis of clinical tests (28,35).

Reliability of the clinical tests in predicting the presence or absence residual neuromuscular block in comparison to the "gold standard" has been investigated in a few studies. The most commonly used tests prior to extubation are the presence of adequate ventilation and a sustained head lift.(1) At a level of neuromuscular recovery that allows for adequate ventilation in a patient whose trachea is intubated, the muscles responsible

for maintaining airway patency and protection are significantly impaired.(36) A study done by Pederson et al in 1990 showed that 16 out of 19 subjects could sustain a 5 second head lift with a TOF ratio of less than 0.5.(37) Eikermann et al also observed that majority of subjects could sustain a head lift for 5 seconds with a TOF ratio < 0.5.(2). Other commonly used clinical tests, such as sustained leg lift, hand grip, smile swallow and speak, have all been shown to have poor sensitivity in predicting residual neuromuscular block. (Table 1) (3, 4) The ability to sustain a tongue depressor(or a bite block or oral airway) between a clenched jaw was suggested as a more sensitive test to exclude residual neuromuscular block , after discovering it in studies with awake volunteers (33) but a similar sensitivity was not reproducible in the clinical setting.(3, 38)The tongue depressor test seems to be more specific; few patients with a TOF >0.9 are likely to fail this test.(32) Clinical criteria alone, are therefore, clearly inadequate to safely extubate a patient after anaesthesia.

TABLE 1 **Sensitivity, Specificity, Positive, and Negative Predictive Values of**

Variable	Sensitivity	Specificity	PPV	NPV
Inability to smile	0.29	0.80	0.47	0.64
Inability to swallow	0.21	0.85	0.47	0.63
Inability to speak	0.29	0.80	0.47	0.64
General weakness	0.35	0.78	0.51	0.66
Inability to lift head for 5 sec	0.19	0.88	0.51	0.64
Inability to lift leg for 5 sec	0.25	0.84	0.50	0.64
Inability to sustain hand grip for 5 sec	0.18	0.89	0.51	0.63
Inability to perform sustained tongue depressor test	0.22	0.88	0.52	0.64

Individual Clinical Tests(3)

Neuromuscular monitoring

Important terms:

- Supramaximal stimulation :

  The force of contraction of a muscle depends on the number of muscle fibers activated. If a nerve is stimulated with sufficient intensity, all fibers supplied by the nerve will react, and the maximum response will be triggered. For the purpose of neuromuscular monitoring supramaximal stimulus is given, that is, a 15% to 20% greater the electrical stimulus is applied than that necessary for a maximal response, so all the nerve fibers can be stimulated. This can be painful, which is not a concern during anesthesia, but the discomfort of stimulation may be experienced in recovery.

  Brull et al justify the use of sub maximal current in train of four mode of stimulation, as a sub-maximal charge would affect the fourth and first responses proportionately. Therefore, fade in the TOF ratio would be a more specific indicator of residual neuromuscular block. (39–41).

  They also recommended, for routine TOF monitoring, that submaximal, rather than supramaximal charges be employed. As large charges may cause direct muscle stimulation, and, by increasing thumb displacement from the original resting baseline, high charges may lead to overestimation of the magnitude of the fourth TOF response during visual or tactile inspection. The use of a lower current would also offer the added benefit of causing less pain in awake subjects.

Baillard et al also have used a submaximal current of 30 mA in their study of 435 people. Only one patient had a visual analog score of more than three (42)

- Calibration

  Calibration adjusts the gain of the device to ensure that the observed response to supramaximal stimulation is within the measurement window of the device and as close as possible to the "100% control response." The calibration procedure varies with the type of device used, but most often it is done with 1.0 Hz single-twitch stimulation. It is especially important to calibrate when the onset and recovery of the neuromuscular block is established with single twitch stimulation. Device used for objective monitoring of the neuromuscular function should be calibrated before the neuromuscular blocking drug is administered.

  In the TOF mode of nerve stimulation, calibration is considered less important because all four responses are amplified equally. Consequently, the TOF ratio is rarely influenced by calibration; however, in patients with very weak or strong responses to nerve stimulation, one or more responses to TOF stimulation might be out of the recording window, and the displayed TOF response might be incorrect. In some devices, supramaximal stimulation is established concurrently with the calibration procedure.

Patterns of nerve stimulation

The commonly used patterns of nerve stimulation used for monitoring neuromuscular block are Train of four (TOF), double burst stimulation (DBS) and tetanic stimulation with post tetanic count (PTC).

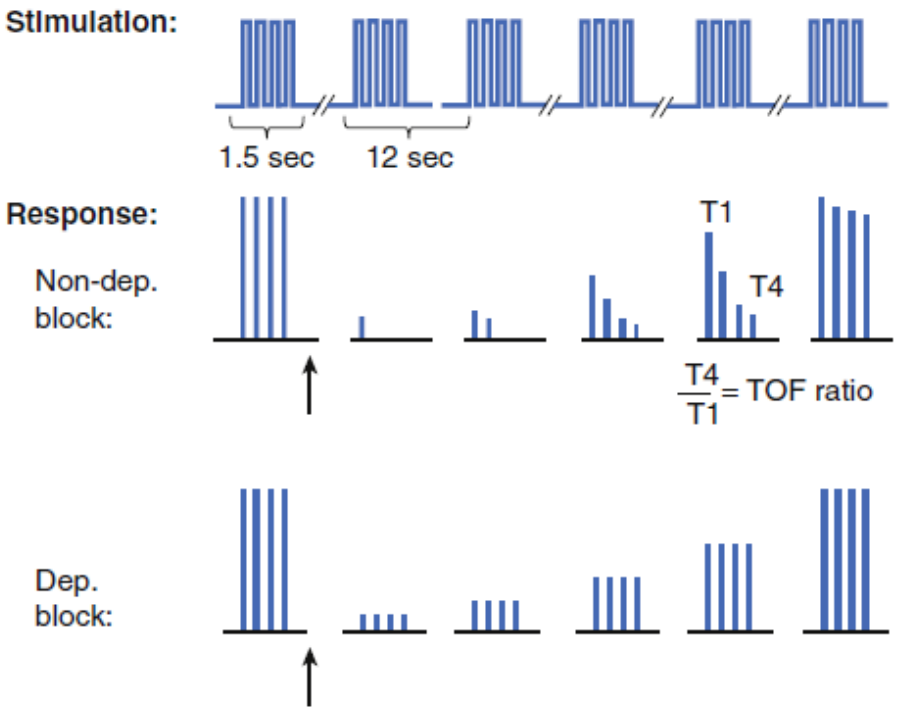
- Train of four stimulation

  Train-of-four nerve stimulation pattern, as introduced by Ali and associates (39, 40) during the early 1970s, consists of four supramaximal stimuli given every 0.5 seconds (2 Hz) (Fig 1). When used continuously, each set (train) of four stimuli is typically repeated every tenth to twentieth second. Each stimulus in the train causes the muscle to contract, and the "fade" in the train of responses provides the basis for evaluation; that is, dividing the amplitude of the fourth response by the amplitude of the first response provides the TOF ratio. All four responses are ideally the same before the administration of a muscle relaxant: the TOF ratio is 1.0. During a partial nondepolarizing block, the ratio decreases (fades) and is inversely proportional to the degree of block. During a partial depolarizing block, no fade occurs in the TOF response; ideally, the TOF ratio is approximately 1.0

  The advantages of TOF stimulation are most apparent during a nondepolarizing neuromuscular block because the degree of block can be read directly from the

TOF response even though a preoperative value is lacking. In addition, unlike double-burst stimulation and tetanic stimulation; it is less painful and also does not generally influence subsequent monitoring of the degree of neuromuscular block.

Figure 3: Pattern of electrical stimulation and evoked muscle responses to train-of-four (TOF) nerve stimulation before and after injection of nondepolarizing (Non-dep) and depolarizing (Dep) neuromuscular blocking drugs

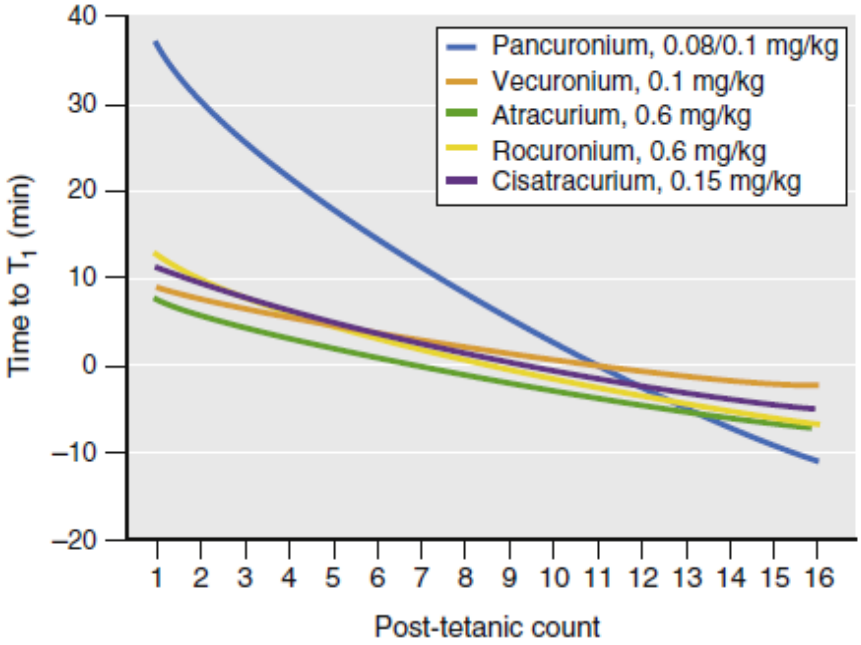


(Figure credit Miller 7th edition)

- **<u>Tetanic stimulation and post tetanic count</u>**

Tetanic stimulation consists of high-frequency delivery of electrical stimuli (e.g., 30, 50, or 100 Hz). Post tetanic count is more commonly used in clinical anesthesia for monitoring of an intense block when single twitch or TOF mode of stimulation cannot be used. A 50-Hz stimulation is given for 5 seconds and the posttetanic response to single-twitch stimulation given at 1 Hz is observed starting 3 seconds after the end of tetanic stimulation (42). During intense block, there is no response to either tetanic or posttetanic stimulation (Fig 2). After the very intense neuromuscular block dissipates the first response to posttetanic twitch stimulation returns and is gradually followed by return of posttetanic twitches until the first response to TOF stimulation reappears. For a given neuromuscular blocking drug, the time until return of the first response to TOF stimulation is related to the number of posttetanic twitch responses present at a given time

Figure 4 :Relationship between the posttetanic count and time when onset of train-of-four (T1) is likely to be elicited for various neuromuscular blocking agents(42)

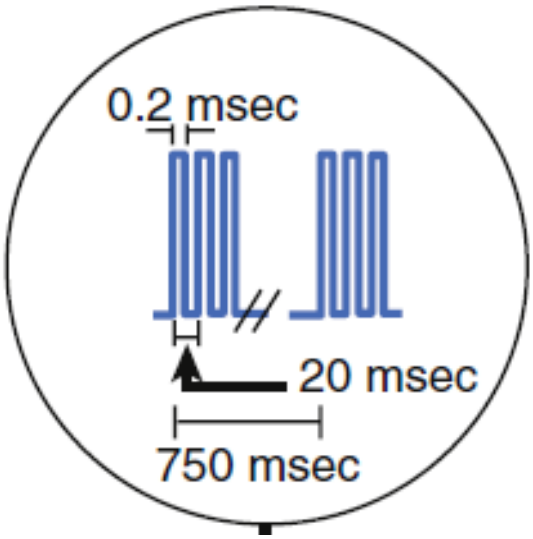


- Double burst stimulation

DBS consists of two short bursts of 50-Hz tetanic stimulation separated by 750 msec, with 0.2-msec duration of each square wave impulse in the burst (Fig 3). The most commonly used number of impulses in DBS is three impulses in each of the two tetanic bursts (DBS3, 3).(43–45)In nonparalyzed muscle, the response to DBS3, 3 is two short muscle contractions of equal strength. In a partially paralyzed muscle, the second response is weaker than the first and corresponds to the typical TOF fade .When measured mechanically, the TOF ratio correlates closely with the DBS3, 3 ratios. DBS was developed with the specific aim of improving manual (tactile) detection of residual block under clinical

conditions,(44)or during recovery and immediately after surgery. DBS3,3response is superior for tactile evaluation of the presence of residual block than the response to TOF stimulation(45)but a manually detected absence of fade in the evaluated response to DBS3,3 (and TOF) does not exclude residual neuromuscular block(46).Hence DBS3,3 cannot replace objective monitoring. However, when objective monitoring is not possible, residual neuromuscular block corresponding to a TOF less than 0.6 or lower can be detected using this method

Figure 5: Double Burst Stimulation (DBS)



(Figure credit Miller 7th edition)

Sites of nerve stimulation

Any superficially located peripheral motor nerve can be stimulated. The ulnar nerve is the most popular site in clinical anesthesia. This is because the muscle itself is easily accessible and has sole innervation from the ulnar nerve, thereby enabling complete assessment of neuromuscular function(47). Other peripheral nerves used for this purpose are the median, posterior tibial, common peroneal, and facial nerves. Muscle groups vary in their sensitivity to muscle relaxants and therefore the results obtained from one muscle group cannot be used for evaluating other muscle groups.

Diaphragm is the most resistant of all muscles to both depolarizing and nondepolarizing neuromuscular blocking drugs.(48,49) In general, the diaphragm requires 1.4- to 2.0-fold as much muscle relaxant as the adductor pollicis muscle for an identical degree of block (49). Also of clinical significance is that onset time is normally shorter for the diaphragm than for the adductor pollicis muscle, and the diaphragm recovers from paralysis more quickly than the peripheral muscles (50).

Similar to the diaphragm, the laryngeal adductor muscles are also more resistant to the commonly used non depolarizing muscle relaxants than the peripheral muscles, like the adductor pollicis. The concentration in the effect compartment producing 50% of the maximum block was significantly greater at the laryngeal adductor muscles than that at the adductor pollicis (51–53). Depolarizing muscle relaxants, however, have been found to have greater neuromuscular block on the laryngeal adductors than the adductor pollicis muscle. The diaphragm is also relatively more resistant to the depolarizing muscle

relaxants than the laryngeal adductors even though the onset times are similar (48,54) . It is suggested, therefore, that the lower margin of safety for neuromuscular transmission in the periphery when compared with that in the faster muscle fibers in the laryngeal adductors may be due to higher receptor density, greater release of acetylcholine, or less acetylcholinesterase activity.

The response of the corrugator supercilii to facial nerve stimulation reflects the extent of neuromuscular block of the laryngeal adductor muscles better than the response of the adductor pollicis to ulnar nerve stimulation (55). Also, the onset of neuromuscular block is significantly faster at the diaphragm and the laryngeal adductors than at the adductor pollicis. Fisher et al hypothesized that more rapid equilibration of the NMBD between the effect site and plasma was reason for this observation (56). These muscles were more centrally located and would have a higher blood flow per unit of tissue which was confirmed by Plaud and colleagues (53). Greater blood flow per gram of muscle at the diaphragm or larynx results in receipt of a higher peak plasma concentration of drug in the brief period of time before rapid redistribution occurs. Therefore, muscle blood flow, rather than a drug's intrinsic potency, may be more important in determining the onset and offset time of nondepolarizing NMBDs.

Greater resistance to neuromuscular blockade accounts for the faster recovery of the respiratory muscles and the muscles of the abdominal wall than at the adductor pollicis. Recovery occurs more rapidly because blood concentration of the NMBD must decrease

more in the muscles of respiration than in the adductor pollicis for recovery of neuromuscular function to begin.

The upper airway muscles seem to be more sensitive than the peripheral muscles (36,57).

The masseter is 15% more sensitive to nondepolarizing NMBDs compared to the adductor pollicis(58). Sundman et al showed that significant upper airway weakness may exist even when the adductor pollicis has recovered to near normal levels. This is why a TOF ratio of greater than 0.9 was required at the adductor pollicis to exclude impaired pharyngeal function, reduced resting tone in the upper esophageal sphincter muscle, and in coordination of the muscles of swallowing, all of which placed the patient at risk of aspiration (8). Patients with TOF less than 0.9 may be weak but able to breathe as long as an endotracheal tube is in place because of the relative resistance of the respiratory muscles. Once extubated, however, they may not be able to maintain a patent airway or protect their airway (12). Patients in post anesthesia care unit (PACU) with a TOF less than 0.9 are more likely to develop respiratory events than those whose TOF ratio is 0.9 or greater because of this reason.

Differences between the TOF ratio measured in both arms have also been noted in the same patient (59,60) . The differences in different muscle groups may be summarized as variations in acetylcholine receptor density, acetylcholine release, acetylcholinesterase activity, fiber composition, blood flow, and muscle temperature.

Qualitative neuromuscular monitoring

The muscle response to various patterns described above can be measured subjectively or objectively. Subjective (qualitative) monitoring of the stimulated response can be done by visual or tactile (by touch) assessment. For detecting residual neuromuscular blockade tactile method was found to be better than visual means though not significantly so. Qualitative means of monitoring offer the advantage of being cheaper as compared to equipment required for quantitative means and are, therefore, more easily available.

The commonly used patterns of neurostimulation as described earlier are TOF, DBS, and tetanic stimulation. Each of these modes has been compared with the gold standard, Mechanomyography (MMG), on the contra lateral arm to detect the reliability of assessing fade.

- TOF ratio :

  Reliability of manual assessment of fade in TOF mode of nerve stimulation was first measured Viby-Mogensen et al in 1985. They observed that fade was detected reliably by the anaesthesiologists only when TOF ratio was < 0.3. Experienced anaesthesiologists detected fade marginally better than inexperienced anaesthesiologists but they were unable to detect fade 80% of the time when TOF ratios were between 0.51 and 0.70. Other studies have also shown that observers are not able to reliably detect fade when TOF ratios exceed 40 (40,43,61)..

- Tetanic Stimulation

  The commonly used 50-Hz tetanic stimulation pattern is the least sensitive qualitative method of monitoring. Fade is reliably detected when TOF ratios are < 0.3(61,62). A 100 Hz stimulating current for 5 seconds has been studied for reliably detecting fade qualitatively. Some studies observed improved detection of TOF ratios of 0.85 to 0.88 using 100-Hz tetanus(61,63) but other investigators have reported no fade at MMG TOF values as low as 0.47(64). Another issue noted with high stimulation rates (> 70 Hz) was that at these high stimulation rates, it neuromuscular fade may occur (detected by MMG) even in the absence of any neuromuscular block because even normal neuromuscular transmission may fatigue (65) Since tetanic stimulation is painful its use is limited to monitoring under anesthesia and not in awake patients.

- DBS

  Subjectively DBS seems to improve detection of residual paralysis compared with qualitative (subjective) TOF monitoring. The threshold for qualitatively detecting fade with DBS is a TOF ratio of 0.60 to 0.70, whereas the threshold with TOF monitoring is 0.40 (45). Clinicians can detect fade better using DBS with respect to TOF maybe because in DBS, 2 successive evoked muscle responses are compared rather than the indirect comparison of the fourth twitch with the first

twitch of TOF. In TOF mode , the comparison of the fourth to the first twitch is likely made difficult by the second and third twitches (39)

Hence we can conclude that qualitative neuromuscular monitoring is not sufficient to reliably exclude residual neuromuscular block in the post anaesthesia care unit.

INSTRUMENTS FOR RECORDING EVOKED RESPONSES

- **Mechanomyography**

  Mechanomyography (MMG) measures isometric muscle contractions (force of contraction) in response to nerve stimulation. MMG quantitatively measures isometric contraction of the adductor pollicis usually in response to ulnar nerve stimulation. The thumb is placed on the force transducer under mild tension, with a preload of 200 to 300g, to produce an isometric contraction and improved evoked responses consistency. The force of contraction is converted to an electrical signal and its amplitude is recorded on an interfaced pressure monitor. The amplitude of the electrical signal is proportional to the strength of the muscle contraction, and measurement of the TOF ratio will yield results that are precise and reproducible. Until the mid-1990s, MMG was used in the majority of clinical studies involving NMBDs and has been considered the “gold standard” method of assessing evoked responses(66).

Disadvantages:

- Bulky equipment used mostly in research and pharmacodynamic studies.
- No commercially available monitor for clinical setting.

- **Electromyography**

  Evoked EMG records the electrical activity of the corresponding muscle (compound muscle action potential) using recording electrodes after nerve stimulation. It allows on-line analysis and graphical display of the evoked response. The rationale behind EMG monitoring of neuromuscular block is the fact that changes in force of contraction of a muscle are proportional to the changes in the compound muscle action potential. New sites for recording EMG responses are the diaphragm and vocal cords (67,68). Although the results of measurements from EMG and MMG correlate well, these cannot be used interchangeably (44).

  Disadvantages:

  - Tedious to set up even though it is less bulky than MMG.
  - Electrocautery interferes with recording limiting its uses in the operation theatre.
  - Direct muscle stimulation will lead to false results.

- **Piezoelectric neuromuscular monitors**

  The technique of the piezoelectric monitor is based on the principle that stretching or bending a flexible piezoelectric film (e.g., one attached to the thumb) in response to nerve stimulation generates a voltage that is proportional to the amount of stretching or bending. The limited data available suggest good correlation between PZEMG, MMG and AMG, but variation in values obtained can be present (69,70)

- **Phonomyography**

  Contraction of skeletal muscles generates intrinsic low-frequency sounds, which can be recorded with special microphones (acoustic myography). This method has been evaluated for clinical and research purposes. Several reports indicate good correlation between evoked acoustic responses and those obtained with more traditional methods of recording, such as MMG, EMG, and AMG(71–73). Theoretically, the method can be applied to other muscles of interest such as the diaphragm, larynx, and eye muscle and is easier to use but no commercially available monitors are available so far.

- **Acceleromyography**

  The acceleromyographic method of monitoring neuromuscular block is based on Newton's second law of motion: force = mass x acceleration (74). When the mass (the thumb for example) is constant, the acceleration is directly proportional to the force.

  The acceleration is measured using a small piezo-electric ceramic wafer. Exposure of the electrode to a force generates an electrical voltage proportional to acceleration of the electrode. The most common site for monitoring acceleration is the adductor pollicis muscle, but other muscles such as the hallucis brevis, orbicularis oculi and corrugator supercilii have also been used.

  When AMG is used with a free-moving thumb, wide limits of agreements in twitch height (T1) and TOF ratio and differences in the onset and recovery course of block between AMG and MMG have been found. The AMG control TOF ratio also is consistently higher than when measured with a MMG transducer. In accordance with this, several studies have indicated that when using AMG, the TOF ratio indicative of sufficient postoperative neuromuscular recovery is 1.0 rather than 0.90, as when measured by MMG or EMG in the adductor pollicis muscle(2,38,61,75).

  In AMG, the control baseline TOF value prior to administration of a neuromuscular blocking drug is most often 1.1 to 1.2 , and in some patients is as high as 1.4. This probably indicates that the TOF ratio necessary for excluding residual block would be equally higher. A TOF ratio of 90% of baseline control

TOF value would actually suggest adequate recovery. This process is called normalization. Currently, no commercially available monitors can “normalize” the TOF ratio automatically. Therefore, for excluding residual block using AMG, a TOF ratio of at least 1.0 should be targeted to exclude residual block(61,76–78).

Because AMG is prone to errors as a result of artifacts, unstable twitch responses and movements (including those caused inadvertently by the surgeon or other personnel in the operating room) more often than MMG and EMG, it is advised to fix the fingers and the forearm when the thumb is used for AMG monitoring.

Several studies have indicated that objective monitoring with AMG reduces and almost eliminates the problem of postoperative residual neuromuscular block. (76,79–81)

WHAT IS THE INCIDENCE OF RESIDUAL NEUROMUSCULAR BLOCK?

TOF ratio <0.7

Viby-Mogenson et al, in1979, were among the first ones to study the incidence of residual neuromuscular block in the post anaesthesia care unit. 42% of their patients had a TOF ratio less than 0.70 and 24% were unable to perform a 5-second head lift on arrival to the PACU. They concluded that , for reversing neuromuscular blockade, the average dose of Neostigmine given (2.5 mg) was insufficient (82).

Subsequent studies demonstrated that use of long acting NMBDs was associated with similarly frequent incidence of residual neuromuscular block ; TOF ratios less than 0.70 were found in 21% to 50% of patients in the early postoperative period(83,84) .When the long acting relaxants were compared with intermediate acting ones, it was also observed that, the risk of postoperative residual blockade was considerably lowered if intermediate-acting NMBDs were used (31,85,86). Many investigators assumed that the incidence of residual blockade would reduce considerably in the PACU, as the use of long-acting NMBDs began to decrease in the operating room.

TOF ratio <0.9

Around the early 2000's a lot of studies were published which claimed that instead of TOF <0.7 a TOF <0.9 should be taken as the cut off for reliably assuming that a patient has residual neuromuscular block or not. This was based on the fact that upper airway

obstruction , pharyngeal muscle in coordination and other symptoms of muscle weakness was present in subjects with a TOF ratio of less than 0.9 (2,8,9,33,34). TOF ratio greater than or equal to 0.9 became the "gold standard" to exclude residual neuromuscular block.

Studies done in a large number of patients (150 to 640) have demonstrated that approximately 31% to 50% of patients have clinically significant residual neuromuscular blockade with adductor pollicis TOF ratios less than 0.90 following surgery(3,4,38).

Naguib and colleagues did a meta-analysis, in which data from 24 clinical trials was collected and the incidence of residual blockade by NMBD type and TOF ratio was calculated. The observed incidence of postoperative residual blockade varied widely between studies, ranging from 5% to 93% based on a number of factors. The pooled rate of residual blockade, defined as a TOF ratio less than 0.90, was 41% when studies using intermediate-acting NMBDs were analyzed.(84)

Factor affecting the presence or absence of residual neuromuscular block

A number of factors may influence the degree of residual block. The observed incidence of residual blockade is more frequent if a threshold definition of 0.90 is used (versus the previous threshold of 0.70). Similarly, a frequent incidence of residual paralysis is observed if there is a short time interval between reversal of NMBDs and quantification of TOF ratios (TOF ratios measured at the time of extubation versus measurement in the PACU).(87) Furthermore, the technology used to quantify neuromuscular recovery may

influence the percentage of patients with TOF ratios less than 0.90 following surgery. For example, when compared with mechanomyography (MMG), AMG frequently overestimates the degree of neuromuscular recovery.(61)

Depth of Neuromuscular Blockade at the Time of Reversal.

The depth of neuromuscular block at the time of reversal of block is the primary anesthetic management variable determining the effectiveness of anticholinesterase antagonism. Administration of anticholinergic agents during intense neuromuscular block is a not advisable and some evidence of spontaneous muscle recovery should be present prior to reversal. Early administration during intense neuromuscular block offers no advantages and in turn delays recovery. (88–90)

The time required to achieve a TOF ratio of 0.90 after anticholinesterase administration is significantly shorter when a higher TOF count is present at reversal. In separate studies done by Kirkegard et al in 2002 and Kim et al in 2004, it was observed that the time taken for TOF to be greater than 0.9 was significantly higher in patient who were reversed when TOF count was 1 than when it was 4. In both investigations, a large inter individual variability in reversal times was observed. (91, 92)This is likely a reflection of the individual response to the NMBD administered. The reason for marked prolongation of reversal times in some patients (up to 143 minutes) was not determined, but may be due to the “ceiling effect” with respect to the blockade (peak effect of the antagonist is followed by a plateau phase in which the balance between diminishing anticholinesterase activity and spontaneous recovery determines the slope of the recovery curve.

Time interval between anticholinesterase administration and tracheal extubation.

As noted in the studies by Kirkegard and Kim, on an average 15 minutes were taken if there were 4 twitches on TOF stimulation and around 20 to 30 minutes if 1 to 3 twitches were present.(91,92) It is suggested therefore that, to ensure patient safety, anticholinesterase drugs should be given on average 15 to 30 minutes before the anticipated extubation in the operating room.

Type of NMBD used intraoperatively (Long-Acting versus Intermediate-Acting).

A number of studies, including a Meta analysis by Naguib et al have demonstrated that use of long acting muscle relaxants is associated with increased incidence of residual neuromuscular block as compared to intermediate acting muscle relaxants. (84)

Type and Dose of Anticholinesterase.

Neostigmine, Edrophonium, or Pyridostigmine appear to be similarly efficient at reversing moderate levels of block though Edrophonium appears to be slower at reversing a deep block.(93, 94) Usually larger the dose, faster and more complete is the reversal. This is true only till the maximal dose of anticholinesterase has been administered as acetylcholinesterase is maximally inhibited. Any further dose after this will have no effect. The maximal dose for Neostigmine is 0.06 to 0.08 mg per kg and Edrophonium is 1 – 1.5 mg per kg.(89)

Age

Older patients have altered responses to NMBD's due to reduction in organ function as well as changes at the neuromuscular level. The concentration and half life of anticholinesterases are also prolonged in the elderly because of reduced clearance. The increased plasma concentration of anticholinesterases leads to increased duration of action for both Neostigmine and Pyridostigmine, but not Edrophonium.(95,96)

Type of Anesthesia.

Volatile anesthetics vs. intravenous anaesthesia

Volatile anesthetics intensify the action of nondepolarizing NMBDs when compared with intravenous anesthetics.(92,97)

Continuous Infusion versus Bolus Administration of NMBDS

. Recovery from neuromuscular blockade may also be influenced by whether an infusion was used or intermittent boluses were given.

Renal Function.

Renal excretion accounts for 50% to 75% of plasma clearance of Neostigmine, Pyridostigmine, and Edrophonium. Renal excretion of anticholinesterase is reduced similar to NMBDs and therefore management of patient with normal or impaired renal function should be similar.

Acid-Base Status.

Only laboratory studies have been done to evaluate the influence of metabolic status and respiratory acid-base balance on reversal of neuromuscular blockade.

Miller et al s research suggests that recovery may be delayed in the presence of respiratory acidosis and metabolic alkalosis.(98) These problems are worsened in the recovery room due to hypoventilation due to the action of intraoperative drugs like inhalational agents and opioids.

Neuromuscular Monitoring.

Qualitative and quantitative neuromuscular monitoring should be used to guide dosing of both NMBDs and their reversal in the operating room. (Fig 6-7)

Patients with Cholinesterase Deficiency.

The duration of neuromuscular blockade following the administration of either succinylcholine or mivacurium is prolonged in patients with atypical plasma cholinesterase enzyme.

Figure 6 and 7 suggest how to use objective and qualitative neuromuscular monitoring in daily anesthesia practice.(99)

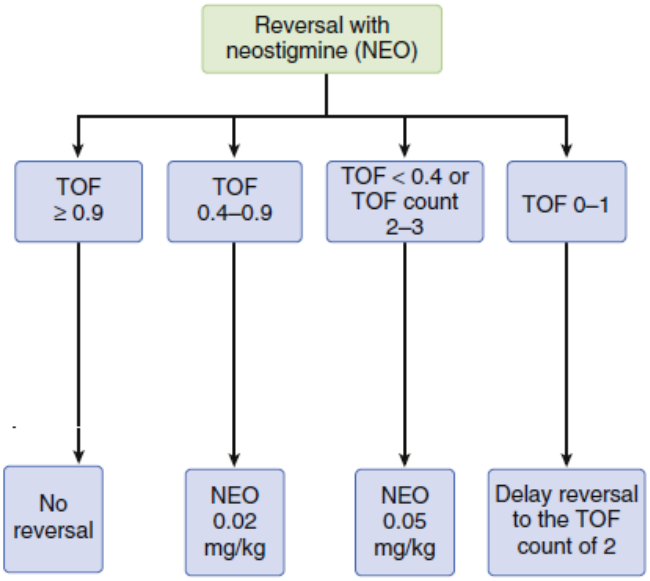


Fig6: When quantitative (objective) neuromuscular monitoring is present

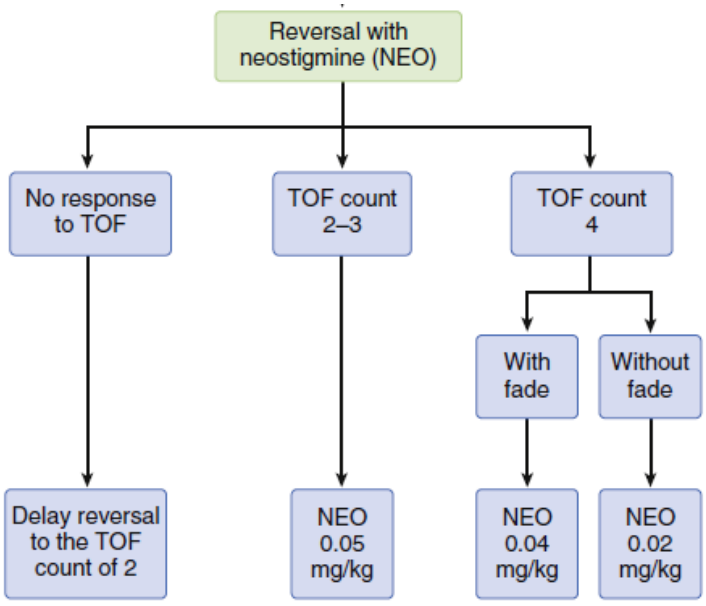


Fig7: When qualitative(subjective) neuromuscular monitoring is present or quantitative is unreliable(99)

PROBLEMS OF RESIDUAL NEUROMUSCULAR BLOCK

The fact that use of NMBDs is associated with significant adverse effects was observed in 1959 when, Beecher and Todd, in a landmark investigation examining mortality rates in 599,548 surgical patients undergoing procedures between the years 1948 and 1952 observed there was a six fold increased risk in mortality in the perioperative period, when neuromuscular blocking drugs were used.(100)

Multiple other large scale studies have been published between 1965 and 1990, which have examined the perioperative complications due to anesthetic techniques. Audits done in South Africa and Great Britain have also implicated muscle relaxants use to a higher morbidity and mortality.(101,102)

More recent studies have continued to demonstrate an association between adverse outcomes and residual neuromuscular blockade. Large scale studies in the Mayo clinic and a case control study done in the Netherlands have also shown an association of the same.(103,104)

In retrospective and prospective observational trials, associations may be identified but causality cannot be established definitively. In particular, the presence of residual neuromuscular block was not objectively demonstrated using quantitative neuromuscular monitoring in these investigations. Therefore, it is difficult to determine with certainty that the residual effects of NMBDs directly contributed to the adverse outcomes analyzed.

Volunteer studies

In clinical studies it is difficult to differentiate the adverse physiologic effects resulting from incomplete neuromuscular recovery from the residual effects of opioids, benzodiazepines, volatile anesthetics, or anesthesia induction drugs.(32) Upper airway obstruction and ventilatory depression may secondary to any of the intra operative used drugs or due to residual block. Volunteer studies helped in removing the confounding factor of these drugs to study the effects of residual neuromuscular block better. In these investigations, intermediate-acting relaxants were titrated to various TOF values in awake subjects, and the physiologic effects of small degrees of neuromuscular block were determined in the absence of other anesthetic drugs. The results of various studies are tabulated in Table 3.

Table 2

Volunteer studies
Impairment of pharyngeal coordination and force of contraction (MMG TOF ratio 0.8)(8,9)
Swallowing dysfunction/delayed initiation of the swallowing reflex (MMG TOF ratio 0.8)(8)
Reductions in upper esophageal sphincter tone (MMG TOF ratio 0.9)(8)
Increased risk of aspiration (MMG TOF ratio 0.8)(9)
Reductions in upper airway volumes (AMG TOF ratio 0.8)(105)
Impairment of upper airway dilator muscle function (AMG TOF ratio 0.8)(105)
Decreased inspiratory air flow (AMG TOF ratio 0.8)(2)
Upper airway obstruction (AMG TOF ratio 0.8)(2)
Impaired hypoxic ventilatory drive (MMG TOF ratio 0.7)(103–105)
Profound symptoms of muscle weakness (visual disturbances, severe facial weakness, difficulty speaking and drinking, generalized weakness (AMG TOF ratios 0.7–0.75)(106)

Clinical studies in post operative patients

Table 3

Clinical studies in surgical patients
Increased risk of postoperative hypoxemia (AMG TOF < ratio _0.9)7,26 Increased incidence of upper airway obstruction during transport to the PACU (AMG TOF ratio _0.9)6 Higher risk of critical respiratory events in the PACU (AMG TOF ratio < 0.9)6,7 Symptoms and signs of profound muscle weakness (pancuronium versus rocuronium)26,53 Delays in meeting PACU discharge criteria and achieving actual discharge (AMG TOF ratio _0.9)26 Prolonged postoperative ventilatory weaning and increased intubation times (cardiac surgical patients) (AMG TOF ratio> 0.9)53 Increased risk of postoperative pulmonary complications (atelectasis or pneumonia) (MMG TOF ratio _0.7)5

STUDIES FROM INDIA

Only limited data could be obtained on literature search owing to less number of studies done in India on the topic. A study done by Kumar et al on 150 patients , studied the incidence of RNMB with 3 commonly used muscle relaxants and the effect on pulmonary function test in the immediate post-operative period (107). .Neuromuscular monitor (TOF watch® Organon Ltd., Dublin, Ireland) was used. 57% of the patients had RNMB on arrival to recovery room (TOF <0.9) with a mean time of 15 minutes to recover (TOF>0.9).The type of relaxant used did not have any statistical significance on the incidence of RNMB or PFT. They also found that the post-operative PFT was significantly reduced (40% to 60%) which add to the post operative morbidity.

Another study done on incidence of RNMB with Rocuronium and Vecuronium, found that there is an increased chance of RNMB with Rocuronium (33%) compared to Vecuronium (17%) which was found to be statistically significant.(108)

Joshi et al studied the compared the effect of Neostigmine on RMNB in normal weight, over weight and obese females. It was seen that recovery of TOF to > 0.7 was delayed in overweight and obese patients(109).

MATERIALS AND METHODS

a. **Setting:**

This prospective study was conducted in the post anesthesia care unit of Christian Medical College, Vellore, Tamil Nadu, and India...

The department of Anaesthesia facilitates surgical and outpatient procedures to approximately 100 patients per day. The variety of procedures covered includes general surgery, orthopaedics, gynaecology, paediatrics, urology, neurosurgery, spine and ENT to name a few.

Around 50 percent of our patients receive general anaesthesia and almost all are extubated except patients undergoing cardiothoracic or neurosurgeries.

We have four recovery rooms attached to the operation theatre block, which receive postoperative major and minor cases after surgery.

Adult patients receiving muscle relaxants during surgeries will be eligible to participate.

b. Study design:

It was a prospective observational study to determine the incidence and risk factors of residual neuromuscular blockade among patients coming for elective surgical procedures receiving intermediate acting muscle relaxants.

c. Participants:

Inclusion criteria:-

Adult patients (ASA 1 to 3) undergoing surgical procedures under general anesthesia receiving intermediately acting neuromuscular blocking drugs were eligible for this study.

Exclusion criteria:-

- Patient refusal or unable to give consent

- <18 years and > 80 years
- Pre existing neuromuscular disease
- Patients receiving long acting muscle relaxants
- Patients with planned post operative ventilation

The anaesthetic technique during the surgery was not altered. The conduct of anesthesia including the choice of muscle relaxant, reversal and use of neuromuscular monitoring was at the discretion of the concerned anesthetist.

d. **Variables:**

Residual neuromuscular blockade was defined as a TOF ratio of <1

Adverse respiratory event is defined as

1. Oxygen saturation < 90% on Oxygen by face mask at 6 l/min.
2. Upper airway obstruction or visible noisy breathing requiring
    a. Manoeuvres like chin lift, jaw thrust
    b. Airway adjuncts : oral or nasal airway
    c. Re intubation

Duration of discharge from recovery was defined as the time interval between the patient coming into recovery and the time at which the patient left the recovery room, as recorded by their nurses who transferred them.

e. **Data Sources/measurement:**

Residual neuromuscular blockade was measured using TOF watch SX.

Saturation was measured by standard plethysmography.

Temperature was measured by a digital thermometer in the axilla.

f. Sample size:

Sample size was calculated using the formula $4pq/d^{2:}$

Expected prevalence (p) being around 30 %, and taking (d) as 5 (16% of p) we arrived at the sample size as 336.

g. **Statistical methods:**

The incidence of TOF ratio <1 was calculated.

Patients were divided into 2 groups based TOF ratio <1 or ≥ 1. Secondary outcomes and demographic variables were compared in the two groups.

Intraoperative factors such as duration of surgery, total dose of relaxant, choice of relaxant, time from last dose to reversal of paralysis, time from reversal to extubation, dose of reversal were compared.

h. Methodology

The study was approved by the Institutional review board and ethics committee of Christian Medical College, Vellore and was internally funded by Fluid research Grant of Christian Medical College, Vellore.

195 patients coming for elective surgical procedures were recruited for the study during Feb 2015 to Aug 2015. The patients received standard care during the intraoperative period according to according to the discernment of the concerned anaesthetist.

On arrival into recovery room, the routine monitoring of vital signs was done. All patients after general anaesthesia received oxygen by face mask at 6 l/min. The patient was then evaluated for ability to sustain 5 second head lift and hand grip. The presence of airway adjunct while shifting was noted. Any noisy breathing or signs of upper airway obstruction like tracheal tug or snoring were observed and corrected with airway manoeuvres, or airway adjuncts. Axillary temperature was noted at this point.

The patients arm was placed extended on a cushioned arm board and fastened with 2 inch Velcro straps around the forearm and four fingers. (Fig 5) Free mobility of the thumb was ensured.

2 surface electrodes were applied, after cleaning the volar aspect of the forearm the distal electrode was placed approximately 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the radial side of the tendon to the flexor carpi ulnaris muscle. The other electrode was placed 3 – 6 cms proximally.

The TOF Watch SX was calibrated at 30 mA stimulus intensity in calibration mode 1 of the TOF watch. Once the instrument was calibrated, measurements were taken 15 seconds apart until 2 consecutive values were within 10 % of each other.

The average of these two was taken as the TOF ratio and the average was rounded off to the lower whole number, Example: 96.5% became 96%.

If TOF ratio was less than 1, readings were taken 10 minutes apart till it was greater than 1.

If any signs of upper airway obstruction were present, and two consecutive readings were less than 0.7, the concerned anaesthetist was informed and 0.02 microgram per kg of Neostigmine was given up to a maximum of 0.07 microgram per kg.

The intraoperative details were noted from the anaesthesia record and time to discharge was noted from the patient record register.

Figure 8: Positioning of electrodes and the transducer on the thumb

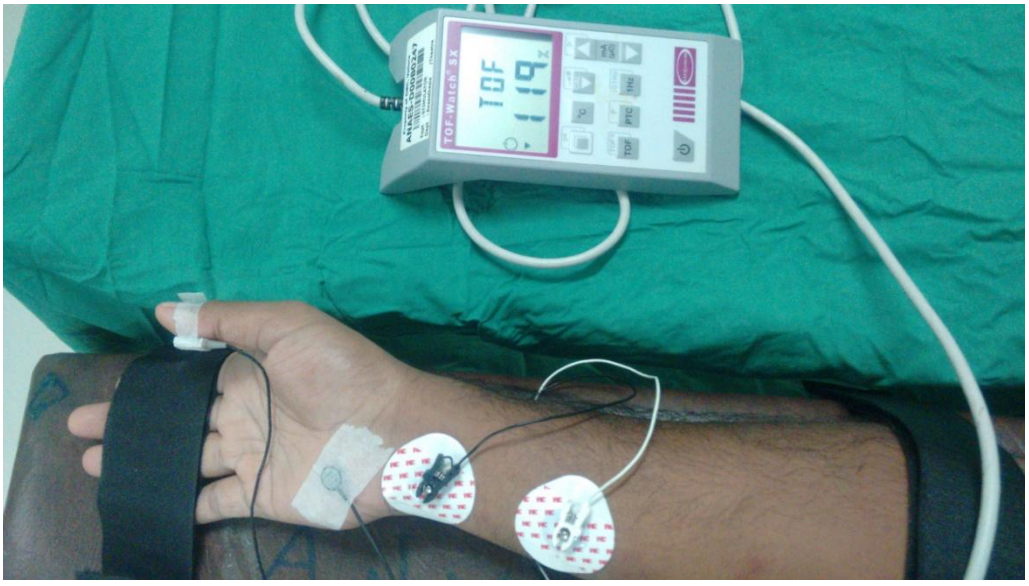


Figure 9: A TOF ratio after calibration

i. Statistical analysis

All baseline variables are expressed in terms of mean ± standard deviation if they are continuous variables. All categorical variables are reported using frequencies and percentages. If the distributional assumption satisfies normality, then the measurements expressed as mean and standard deviations. If there any doubt of normality, Shapiro Wilk's test was performed to check for normality assumption and then median with inter quartile range will be reported. The comparison of the two groups was done using t-test if the assumption of normality holds good. If not, Mann Whitney U test used to compare between the groups. ANOVA will be used to compare more than two groups. Chi-square test was done to find the association between outcome and their risk factors. Multivariate analysis was done using multiple logistic regressions. All the analysis was done using SPSS (version 18).

RESULTS

INCIDENCE

A total of 195 cases were included in the study, from which eight (4.1 %) were excluded from the final analysis as the TOF ratio could not be measured because of shivering or lack of patient cooperation.

The incidence of residual neuromuscular block as defined by various TOF ratios is depicted in Table 4.

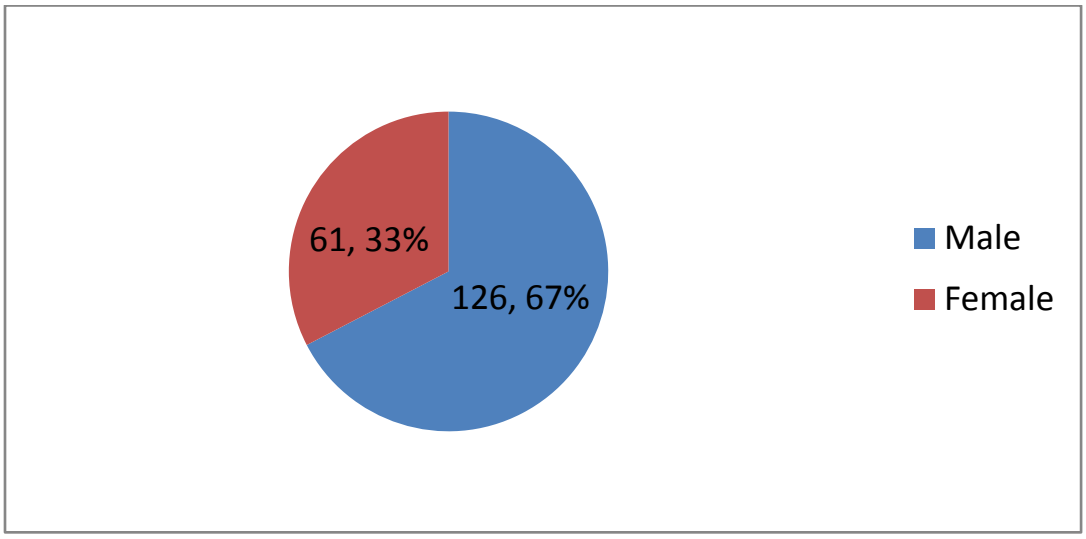
TOF ratio less than	Number of participants (N= 187)	%
0.7	4	2.13%
0.9	59	31.55%
1	96	51.33%

Table 4

For further analysis the study population will be divided on the basis of TOF ratio by the presence of RNMB (TOF <1) and absence of RNMB (TOF >/= 1)

GENDER

Gender distribution of the 187 participants studied is shown in Fig 1.



Gender	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	n	%	n	%	
Male	69	54.8%	57	45.2%	**0.016**
Female	22	36.1%	39	63.9%	

Table 5

There is an increased incidence of RNMB in females as compared to males and the difference appears statistically significant.

BMI

Two patients weight were not documented as they were unable to stand. The relationship of BMI of the 185 participants with the TOF ratio is documented in Table 3. We can see that a higher percentage of patients among the obese and overweight group were likely to have RNMB.

BMI	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	n	%	n	%	
Normal	68	54.8	56	**45.2%**	
Overweight	15	34.9%	28	**65.1%**	**0.033**
Obese	6	33.3%	12	**66.7%**	

Table 6

GENDER versus BMI

Table 7 shows that females were more likely to be obese or overweight than their male counter parts.

BMI	Male		Female		P value
	n	%	n	%	
Normal	96	77.4%	28	45.9%	**0.001**
Overweight	24	**19.3%**	19	**31.1%**	
Obese	4	**3.3%**	14	**22.9%**	
Total	124	100%	61	100%	

Table 7

ASA status

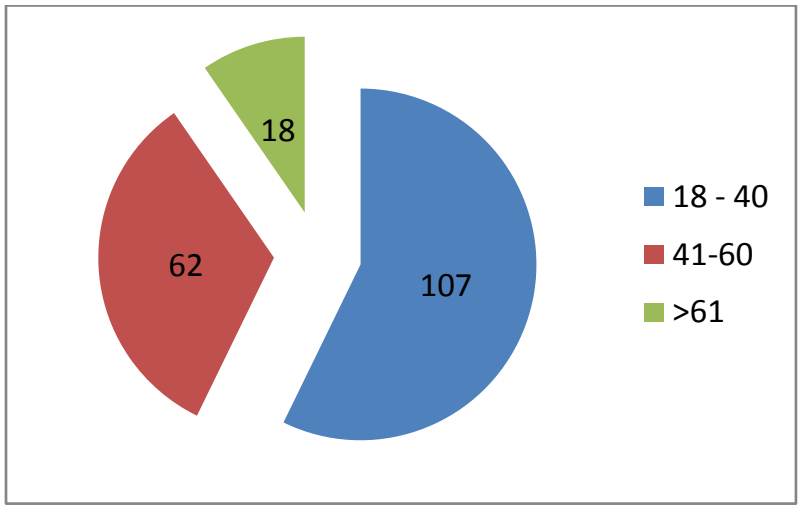
No statistically significant difference was observed among the ASA status of the patient and presence or absence of residual neuromuscular blockade.

ASA	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	n	%	N	%	
I	73	50%	73	50%	0.73
II	17	44.7%	21	55.3%	
III	1	33.3%	2	66.7%	

Table 8

AGE

The age distribution of our population is shown in Fig 11.



AGE	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	n	%	N	%	
< 60	8	47.06%	9	52.94%	0.89
≥60	83	48.82%	87	51.18%	

Table 9

Age was not identified as a risk factor

PROCEDURE TYPE

The patient distribution across various specialties is described in Table 10. ENT and general surgery patients constituted a major part of the population studied.

Department	Number	Percentage
ENT	50	26.7%
General Surgery	56	29.9%
Orthopaedics	24	12.8%
Urology	28	15.0%
Spine	12	6.4%
Gynaecology	5	2.7%
Others	12	6.4%

Table 10

INTRAOPERATIVE VARIABLES

Agent used for maintainenance

Isoflurane was the most commonly used agent for maintainenance and no significant difference was found on the basis of inhalational agent used (Table 11)

Agents used	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	N	%	N	%	
ISOFLURANE	87	49.2%	90	50.8%	
SEVOFLURANE	2	28.6%	5	71.4%	0.46
DESFLURANE	2	66.7%	1	33.3%	

Table 11

Use of Succinylcholine

SUCCINYLCHOLINE USED	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	N	%	N	%	
NO	79	52%	73	48%	0.059
YES	12	34.3%	23	65.7%	

Table 12

Intra operative use of succinylcholine prior to using non depolarizing muscle relaxants showed a higher frequency of residual neuromuscular block (65.7%) as compared to patients in whom it was not used (48%), though it was not statistically significant ($p > 0.05$).

Type of intermediate acting relaxant used

RELAXANT	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	N	%	N	%	
ATRACURIUM	40	53.3%	35	46.7%	0.408
VECURONIUM	50	46.3%	58	53.7%	
ROCURONIUM	1	25%	3	75%	

Table 13

Vecuronium was the most common relaxant used intra operatively in 108 participants (57.8%), followed by Atracurium in 75 (40.1%) and Rocuronium in 4 (2.1%). The incidence of RNMB was not significantly different in atracurium and vecuronium groups.

Total dose of relaxant

Relaxant	Total dose in mg		Total dose per kg bodyweight	
	Mean dose ± SD (mg)	P value	Mean dose ± SD (mg/kg)	P value
Atracurium				
TOF >=1	31.4 ± 18.4	0.29	0.50± 0.33	0.27
TOF <1	35.4 ± 18.3		0.58 ± 0.33	
Vecuronium				
TOF >=1	7.14 ± 1.9	0.46	0.12 ± 0.33	0.46
TOF <1	7.71 ± 2.8		0.12 ± 0.31	
Rocuronium				
TOF >=1	110.0 ± 0	0.34	1.69 ± 0.0	0.63
TOF <1	80.00 ± 30		1.34 ± 0.59	

Table 14

The total dose of the relaxant given and the total dose per kilogram body weight are also compared with the presence or absence of residual block and are shown in Table 14.

Dose of reversal given

	Total Neostigmine dose in mg		Total Neostigmine dose per kg bodyweight	
	Mean dose ± SD (mg)	P value	Mean dose ± SD (mg/kg)	P value
TOF >=1 TOF <1	2.52 ± 0.16 2.49 ± 0.29	0.446	0.042± 0.01 0.041 ± 0.01	0.571

Table 15

There was no significant correlation between the total doses of Neostigmine given or Neostigmine dose calculated to per kg body weight.

Time interval between Time of measurement of TOF and intra operative events

Time intervals		Time interval in minutes	
		Mean time ± SD (minutes)	P value
Procedure time	TOF >=1 TOF <1	178.5 ± 10.7 188.7 ± 9.6	0.48
Time of Last dose to reversal	TOF >=1 TOF <1	101.0 ± 62.6 95.3 ± 64.1	0.53
Time of Reversal to measurement	TOF >=1 TOF <1	37.9 ± 14.0 37.1 ± 12.1	0.68
Time of last dose to measurement	TOF >=1 TOF <1	138.9 ± 67.6 132.4 ± 64.6	0.50

Table 16

The various time intervals between the two groups are shown and they are not statistically significant. The mean time interval from reversal to extubation was 12.7 ± 6.6 minutes in all patients and the mean time from extubation to measurement of TOF ratio was (24.8 ± 10.2) minutes which was comparable in those with and without RNMB (23.9 ±8.50 vs. 25.7 ±11.7).

RECOVERY ROOM EVENTS

Incidence of use of airway maneuvers and desaturation

Complication	Frequency N = 187	Percentage
Shifted with airway	52	27.8%
Airway used in recovery	25	13.36 %
Airway maneuvers (Chin Lift, Jaw thrust)	9	4.83%
Saturation less than 90 %	0	0%

Table 17

The distribution of airway related events among the patients having TOF <1 and TOF ≥ 1 is tabulated in Table 9. There is statistically significant use of airway adjuncts in patients with TOF <1 and also they were more likely to be shifted to the PACU with an airway adjunct.

Duration of time spent in PACU

Airway events		TOF				P value
		NO RNMB (>=1)		RNMB (<1)		
		n	%	n	%	
Shifted with airway adjuncts	No	73	54.1%	62	45.9%	**0.017**
	Yes	18	34.6%	34	65.4%	
Chin lift or jaw thrust	No	86	48.3%	92	51.7%	0.672
	Yes	5	55.6%	4	44.4%	
Airway adjuncts required while examination	No	84	51.9%	78	48.1%	**0.026**
	Yes	7	28%	18	72.0%	
Saturation less than 95% in recovery on oxygen	No	91	49.2%	94	50.8%	0.166
	Yes	0	0.00%	2	100%	

Table 18

The mean time spent in recovery room was 103.6 ± 48.6 minutes. Minimum time spent was 20 minutes and maximum time was 260 minutes. The duration of time spent in the recovery time among both groups is documented in Table 10.

Duration of stay in recovery	Mean ± standard deviation (minutes)	P value
TOF <1 TOF>/= 1	109.79 ± 47.98 96.88 ± 48.58	0.071

Table 19

Post operative hypothermia

Temperature in recovery	TOF				P value
	NO RNMB (>=1)		RNMB (<1)		
	n	%	n	%	
>/= 35 º C	89	51.1%	85	48.9%	**0.013**
< 35º C	2	15.4%	11	84.6%	

Table 20

The incidence of hypothermia in our Post Anaesthesia care unit was 6.9%. The hypothermic patients had a higher chance of having residual neuromuscular blockade (84.6 %) as compared to non hypothermic patients (48.9%).

Reliability of clinical tests

Clinical test		TOF				P value
		NO RNMB (>=1)		RNMB (<1)		
		n	%	n	%	
Sustained head lift for > 5 sec	No	28	37.3%	47	62.7%	**0.011**
	Yes	63	56.3%	49	40.1%	
Sustained hand grip > 5 sec	No	23	34.3%	44	43.3%	**0.03**
	Yes	68	56.7%	52	54.2%	

Table 21

The clinical tests are compared with the acceleromyographic TOF ratio in Table 16 and their sensitivity, specificity , positive and negative predictive value to detect residual neuromuscular block as defined by TOF ratio >/= 1 are calculated in Table 21.

	Hand grip >5 sec	Head lift > 5 secs
Sensitivity :	0.458 (0.356, 0.563)	0.49 (0.386, 0.594)
Specificity :	0.747 (0.645, 0.833)	0.692 (0.587, 0.785)
Positive predictive value :	0.657 (0.531, 0.768)	0.627 (0.507, 0.73)
Negative predictive value :	0.567 (0.473, 0.657)	0.563 (0.466, 0.656)

Table 22

Our observation is that inability to sustain hand grip for > 5 seconds is a more specific test than sustained head lift for > 5 seconds for predicting absence of residual neuromuscular blockade.

Table 23: Multivariable analysis for risk factors by logistic regression

Risk Variable	**OR**	**95% CI**	**p- value**
Gender:			
• Male	1.00		
• Female	2.17	1.06 – 4.45	**0.03**
BMI:			
• Normal	1.00		
• Overweight/obese	2.13	1.07 – 4.25	**0.03**
Relaxant:			
• Atracurium	1.00		
• Vecuronium	1.97	0.67 – 5.79	0.22
• Rocuronium	1.65	0.11 – 25.28	0.72
Total dose	1.01	0.98 – 1.04	0.35
Time Interval between			
• Last dose to reversal	0.998	0.99 - 1.004	0.45
• Reversal to measurement	0.997	0.97 – 1.02	0.725
• Total procedure time	1.001	0.99 – 1.005	0.827
Temperature:			
• <35	8.88	1.63 – 48.32	**0.01**
• ≥35	1.00		

DISCUSSION

Despite a good understanding of the neuromuscular physiology, pharmacology and monitoring techniques, residual neuromuscular blockade is a frequent problem in the recovery room. It is associated with significant morbidity. An unpublished study conducted at CMC Vellore in 2000 showed an incidence of RNMB of 28% with a TOF ratio of 0.7. The choices of anesthesia drugs and ventilation modes have changed since then. We wanted to relook at the incidence of RNMB.

We undertook this study to investigate the incidence of residual neuromuscular block in our recovery rooms and to identify the risk factors. We wanted to see whether RNMB was associated with adverse respiratory events.

The reported incidence of RNMB varies from 30 -50%. We based our sample size on a study, which was conducted in our institution, which had an incidence of RNMB of 28 % with a TOF ratio of 0.7. With an expected an incidence of 30% we got a sample size of 336. Recent evidence suggests that TOF ratio of >0.9 corresponds with adequate recovery of pharyngeal muscle function and ventilator response to hypoxia. After collecting 50 patients, we did an interim analysis and found the incidence to be much higher. We recalculated the sample size using 40 % incidence and it came to 150.

After obtaining the permission of Institutional review board, 195 consenting adults were recruited into the study. The mean age of patients with or without residual block was similar without any statistical significance (40.38 ± 14.63 years versus 39.6 ±

13.35years). General surgical (29.9%) and ENT patients (26.7 %) formed the majority of patients studied followed by Orthopaedics and Urology. Other surgeries constituted only a minority of cases (< 6 % each). This could be explained by the fact that patients in these departments were more likely to receive general anaesthesia for facilitation of the procedure than regional anaesthesia.

The incidence of residual neuromuscular blockade in our recovery was found to be 31.5 % with a TOF ratio of less than 0.9 and 51.3 % with a TOF ratio of less than 1. This is comparable to various studies done among other study populations. Other studies done in large study groups ranging from 150 to 640 patients have also found an incidence of 31% to 50% of residual block at the Adductor Pollicis following surgery.(3,4,38) In the meta-analysis done by Naguib et al, which looked at 24 studies published from 1979 to 2005, the incidence of residual neuromuscular blockade varied from 5 to 93 % but the pooled incidence of residual neuromuscular blockade with a TOF ratio less than 0.9 in intermediate acting neuromuscular drugs was 41 %.(84)

Our results also matched the study done by Kumar et al whose incidence was 57 % with TOF ratio of 0.9.

For the purpose of our analysis we took TOF ratio of less than 1 as indicative of residual neuromuscular block. This value is based on multiple recent research articles which suggest that since acceleromyography (AMG) frequently overestimates TOF and to reliably exclude a residual neuromuscular block, a TOF ratio of greater than 1 has to be present. (2,38,61,75)

Analysis of demographic data showed a statistically significant increase in the incidence of residual NMB among females (63.9% versus 45.2%) This was in contrast to a study done in Australia evaluating the incidence of residual neuromuscular blockade where they conclude that patients with residual neuromuscular block were more likely to be male(110).

BMI greater than 25 was shown to be a risk factor. The incidence of Residual neuromuscular blockade was 65.1% in overweight and 66.7 % in obese subjects as compared to 45.2% normal BMI. Weinstein et al demonstrated that increased incidence of residual block in overweight and obese could be because of overdosing and delayed clearance.(111) This idea has also been corroborated by a study done in India , which studied the delay in recovery after Neostigmine reversal in female patients receiving Vecuronium based on their BMI.(109) They found that though the recovery of adductor pollicis muscle strength to a TOF ratio of 0.5 was similar in all the female patients, the recovery was significantly delayed to 0.7 and 0.9 in overweight and obese female patients. The cause of this finding they attributed to dosing of the NMBD based on real body weight and not ideal body weight leading to more redistribution.

Our finding of having increased incidence in females could also be because female patients in our study were more likely to be obese or overweight as compared to their male counterparts. 22.6 % of males and only 54.1% females fell into the high BMI category (table 4), which was statistically significant ($p = 0.00$).

The most common agent used for maintainenance was Isoflurane, followed by Sevoflurane and Desflurane. Although not statistically significant, frequency of RNMB appeared to be more in the Sevoflurane group. Studies done comparing recovery from neuromuscular block in patients receiving inhalational agents and intravenous Propofol concluded that recovery was slower in inhalational agents as compared to Propofol and Sevoflurane slowed it more than Isoflurane. (97) There were no patients who received TIVA in our study population, so its effect on reducing the incidence of RNMB could not be studied. This may be due to the fact that inhalational anesthetics potentiate the action of neuromuscular blocking drugs.(92,97)

There was no significant effect of using succinylcholine before NDMR on residual neuromuscular block. The incidence of residual NMB was lower in the atracurium group (46.7%) compared to vecuronium (53.7%) even though the results were not statistically significant. The incidence was highest in the rocuronium group (3 out of 4 cases 75%), but our numbers were too small to derive any significant conclusion. Butterly et al suggested that residual neuromuscular block was more with Vecuronium than Cisatracurium. (112) Khan et al from India observed that residual block was more common in rocuronium (33%) as compared to vecuronium (17%) (108).Definitive evidence implicating one intermediate acting relaxant over other has not emerged but residual block is more often in long acting relaxants as compared to intermediate acting relaxants, which has led to their reduced usage in clinical practice.(84)

When relaxant subgroups were analyzed based on the total cumulative dose and the total dose per kg body weight, no statistically significant differences were seen. All our patients usually received 2.5 mg of neostigmine irrespective of last dose, also no differences were observed in the mean dose of reversal and mean dose per kilogram in patients with and without neuromuscular blockade. We did not have any data on timing of reversal based on qualitative or quantitative monitoring as it was not a routine practice in our setup. It has been concluded in as early as 1977 than just giving 2.5 mg of Neostigmine is not enough.(82) The timing of reversal is essential because the excess Neostigmine itself can lead to .neuromuscular weakness, manifesting as fade in TOF ratio, hence the dose given has to be modified according to objective neuromuscular monitoring.(99)

The duration of procedure, time from last relaxant to measurement, time of reversal to measurement had no statistical significance in the incidence of residual neuromuscular block. This is in contrast to Yip et al, who found that the incidence was higher in short procedures. The time from last dose of relaxant to reversal was 95.3 ± 64.1 in patients with residual NMB. This duration was high compared to other studies. This may be due to the practice of using PSV Pro mode of ventilation in the GE anesthesia machines towards the end of the procedure. Also cases like ear surgeries, brachial plexus exploration and spine surgeries with monitoring of motor evoked potential minimized the use of intraoperative muscle relaxants and many of these cases didn’t receive any subsequent doses after the initial intubating dose (2 x ED95). The average time between

reversals to extubation was 12.68 ± 6.58 minutes, which is less than the recommended time of 15 to 30 minutes before the planned extubation (91,92). The depth of neuromuscular blockade at which they were reversed is unknown as the TOF count or ratio at reversal was not monitored. The time from reversal to measurement of TOF ratio took 37.4 ± 13 minutes. This duration was comparable to other published studies. Once the handover and baseline monitoring in the recovery were complete, clinical tests to assess RNMB were conducted followed by TOF ratio. The incidence of airway related events were significantly higher among the participants in our study, in particular the use of airway adjuncts. Patients were more likely to have been shifted with an airway or having required an airway adjunct in the recovery room if their TOF ratio was less than 1. Our observations were similar to others who have shown increased use of airway maneuvers and airway adjuncts 65.4% ($p = 0.017$) in patients with residual NMB.(80)

There was no incidence of desaturation in the recovery among the patients studied. As all patients received prophylactic oxygen therapy in the immediate post operative period, the hypoxia may have been masked. However researchers have reported the hypoxia in the post anaesthesia care unit in patients with residual NMB. (13). These observers transferred the patients to recovery without oxygen and measured Oxygen saturation in the recovery and instituted Oxygen therapy if there was desaturation. Our practice is to start all patients on Oxygen and discontinue if they are able to maintain desirable oxygenation after immediate recovery. We did not change this practice as ours was an observational study. This might have masked the true incidence of hypoxia in our study

population. The mean time spent in recovery was 103.6 ±48.6 minutes with a times ranging from 20 minutes to 260 minutes. Though patients with residual neuromuscular block spent a mean time of approximately 13 minutes more than patients without residual neuromuscular block, the difference was not statistically significant. A similar study done by Butterly et al found a statistical difference among time to discharge from recovery room whereas Yip et al did not. (110,112) Many factors could have affected the total time spent by our patient in the recovery. Recovery room nurses call the respective ward once the patient meets adequate criteria for discharge according to Aldrete's score. The availability of the ward attendant, ward nursing staff and distance of the ward from the recovery room could all be contributing factors for the delay in actual discharge of the patient. The time to eligibility of discharge could have been better correlated with the incidence of residual neuromuscular blockade.

Post operative hypothermia, with an axillary temperature less than 35 degree Celsius, was found to be a significant factor affecting the incidence of residual neuromuscular blockade. Hypothermia potentiates the action of neuromuscular blockers and causes delayed recovery. (113,114) Temperature was not monitored intra operatively in 30% of our subjects.

Our study aimed at finding the possible risk factors for RNMB. Univariate analysis showed female sex, high BMI and hypothermia as risk factors for RNMB. Multivariate analysis using logistic regression showed that female gender, BMI more than 25 and post operative hypothermia were the significant predictors. The chances of having RNMB

were doubled in females compared to males (Odds Ratio 2.17, p value 0.03) and overweight and obese individuals as compared to their normal counterparts. (OR 2.13, p value 0.03). Temperature less than 35 increased the chance of RNMB by eight times. (OR 8.8, p value 0.01).

Clinical tests of muscle strength are not very reliable in detecting residual neuromuscular block. Our findings also suggest that the ability to sustained head lift and hand grip for 5 seconds are not enough to exclude residual neuromuscular block. Sustained hand grip appeared to more specific than head lift in predicting absence of neuromuscular block which are similar to results obtained by Cammu et al.(3)

LIMITATIONS

Ours was a prospective observational study. The study was not designed to identify the individual risk factors.

Time to adequate criteria for discharge may have been better parameter than total time spent in recovery to correlate the impact of RNMB on patients in the recovery,

Intra operative variables were documented from the anesthetic record of the patient, so the reliability of the data also depended on the accuracy of monitoring.

Ideally a baseline TOF ratio should be available, prior to administration of muscle relaxants, to normalize the TOF ratio before extubation. This would have created a bias in our study by alerting the anesthetist and hence was not done.

All observations were made by one primary investigator so bias may be present. The clinical tests were done prior to observing the TOF ratio to minimize the bias.

The TOF watch SX is highly sensitive to movement artifacts causing wide variations in successive TOF ratios observed in the same patient. Calibrating the TOF watch improved the precision, but sometimes multiple attempts of calibration had to be made on the same patient. This process becomes more difficult in the immediate post operative period when patients are drowsy, disoriented, shivering and sometimes uncooperative.

CONCLUSION

Residual neuromuscular block defined as a TOF ratio < 0.9 is a significant problem with an incidence of 31%.

Incidence of residual NMB was 51% using the current recommendation of TOF ratio ≥ 1 using accelomyography.

Female sex and patients with BMI > 25 and hypothermia were identified as risk factors for developing residual neuromuscular block.

Patients with residual NMB had significantly high requirement for the use of airway adjuncts.

Clinical test like head lift and hand grip for 5 seconds are not sensitive to reliably exclude residual neuromuscular block.

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ANNEXURES

PROFORMA

Serial no:

Incidence of neuromuscular blockade in the recovery room

Name: Hospital no: Date:

Age: Sex: Weight: Height: BMI:

Sustained head lift possible pre op:

Name of procedure: Total duration of procedure:

Intra operative details:

Total opioids given: Inhalational agent:

Relaxant: Rocuronium VecuroniumAtracurium Succinylcholine

Total dose: Time of first dose

Last dose: Time of last dose

Reversal dose: Time of reversal:

Time extubation:

Neuromuscular monitoring used: yes/ no

Hypothermia: yes/ no/ not used

Drugs:

1. amino glycosides
2. diuretics

co morbid condition:

Time of presentation to Recovery room:

Saturation: Temperature: RR:

Oxygen:

Airway:

Tof ratio in recovery : Time :

Clinical test:

- Sustained head lift
- Sustained hand grip

Airway obstruction : yes/ no

Maneuver required: Time of calling ward :

- Airway maneuver: yes/ no
- Airway adjuncts : yes/ no
- Reintubation : yes / no

Additional reversal given: yes/ no

	5min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min
TOF RATIO												

ANNEXURE II WRITTEN INFORMED CONSENT FORM

Date:

Study title: Incidence of residual neuromuscular blockade in the recovery room among patients receiving intermediate acting neuromuscular blocking drugs.

It has been explained to me by the investigator in the language that I understand that this study is being carried to find out residual muscle paralysis among patients shifted to recovery room who are receiving muscle relaxing drugs as a part of general anesthesia. I have been told that it involves monitoring muscle paralysis with an instrument called TOF watch. I have also been told that there is no additional risk in the study. It has been explained to me that I am free to withdraw from the study any time I want and that will not in any way compromise the treatment. I understand that my identity and participation will not be revealed in any information released to third parties.
Subjects' Name
Date of Birth/ Age:

i) I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions
ii) I understand my participation is purely voluntary and that I can withdraw from the study anytime, without any reason, without my medical care being affected.
iii) I understand that my identity will not be revealed in any information.
iv) I agree to take part in the above study.

Signature of subject Date

Name of the subject

Signature of the investigator Date

Name of the investigator

Signature of the witness Date

Name of the witness

PATIENT INFORMATION SHEET

Date:

Study title: Incidence of residual neuromuscular blockade in the recovery room among patients receiving intermediate acting neuromuscular blocking drugs.

The following information is provided to inform you about this study and your participation in it. Please Read the information carefully and you are free to ask any questions regarding the study and the information given. The participation in this study is purely voluntary and you are free to withdraw from the study anytime.

Purpose of the study

Residual muscle paralysis in patients immediately after surgery is estimated to be 30% (that is 30 in 100 people).It is associated with difficulty in breathing, feeling of weakness and respiratory complications . Detecting its presence at the earliest post operatively helps to reduce such airway complications. This study is designed to find out the residual muscle paralysis among patients who are receiving muscle relaxing drugs as a part of general anesthesia after shifting to recovery room with a TOF watch. It will detect the presence of residual muscle paralysis post operatively and therefore in early management of any complications. The results of this study will help in finding out how common this complication is in patients coming to our hospital and the factors responsible for it.

Method to be followed

After shifting to post anaesthesia care unit (recovery room), your blood pressure, pulse rate and oxygen saturation will be checked as is routinely done. Certain instructions will be given to you to follow to clinically assess muscle weakness. Additionally a device will be attached to your hand through which you will receive a small electric current to monitor for signs of residual weakness. If residual weakness is detected or signs of breathing difficulty are found appropriate treatment will be given to you and the small electrical current will be repeated every ten minutes till the test value comes to normal.

Confidentiality

The participation in the study will remain confidential and shall be known only to the investigators.

Withdrawal from the study

Participation in this study is purely voluntary and you can withdraw from the study anytime without any reason. It will not compromise your treatment in any way. There will not be any other risks involved in this study and you need not pay any extra money for the test.

Benefits from this study

The results of this study will help in early detection of residual muscle paralysis and initiate early treatment. It will also helpful to identify how common this problem is and clinicians to be better aware and detect it and thereby improving our standard of care.

DATA SHEET

sno	age	sex	wt	ht	bmi	pde	asa	agt	sch	rel	fd
1	39	1	45	152	19.5	7	1	0	0	2	
2	63	1	75	150	33.3	2	2	0	1	1	
3	45	0	69	162	26.3	4	2	0	0	2	
4	51	0	77	160	30	2	1	0	0	2	
5	40	0	77	164	28.6	2	1	0	0	2	
6	54	1	85	154	35.8	2	2	0	0	2	
7	47	0	62	173	20.7	2	2	0	0	2	
8	62	0	83	175	27	5	2	0	0	2	
9	37	0	50	158	20	4	1	0	0	2	
10	29	1	75	165	27.5	6	1	0	0	1	
11	24	1	58	140	29.5	6	1	0	1	1	
12	30	0	77	165	28.3	3	1	0	0	2	
13	24	1	45	159	17.8	3	1	0	0	2	
14	30	0	60	169	26	3	1	0	0	1	
15	68	1	89	146	42.1	2	2	0	1	1	
16	55	0	65	163	24.5	2	2	0	1	1	
17	33	1	55	156	22.6	6	1	0	0	1	
18	36	1	75	160	29.2	6	1	0	0	1	
19	34	1	85	151	37	6	2	0	0	1	
20	35	0	73	170	24	1	1	0	0	1	
21	18	0	60	175	19.6	1	1	1	0	1	
22	36	0	50	160	19.5	5	1	0	0	1	
23	22	1	56	156	23	2	1	0	0	1	
24	30	0	66	160	25.7	1	1	0	0	1	
25	27	0	63	160	24.6	4	1	0	0	1	
26	18	1	43	153	18.4	1	1	0	0	2	
27	49	0	72	174	23.8	2	1	0	1	1	
28	47	0	70	164	26	2	2	0	0	2	

29	45	1	59	155	24.6	2	2	0	1	2
30	42	1	41	150	18.2	3	1	0	1	2
32	25	0	65	171	22.2	1	1	0	0	2
33	64	0	72	150	31.1	2	1	0	0	2
34	30	0	60	171	20.5	1	1	0	0	1
35	79	0	46	165	16.9	3	2	0	0	1
36	28	0	65	167	23.3	4	1	0	0	3
37	40	1	64	144	30.9	5	1	0	0	2
38	26	0	41	170	14.2	1	1	0	0	2
39	33	1	41	150	18.2	2	1	0	1	1
40	40	1	69	156	28.4	2	1	0	0	2
41	58	0	58	178	18.3	1	1	0	0	2
42	36	0	52	166	18.9	2	1	0	1	1
43	49	0	114	175	37.2	7	2	0	0	2
44	35	0	55	168	19.5	4	3	0	0	1
45	54	0	61	165	22.4	2	1	0	0	1
46	45	0	60	172	20.3	1	1	0	0	1
47	23	0	66	166	24	2	1	0	1	2
48	36	0	69	175	22.5	5	1	0	0	2
49	27	1	48	144	23.1	7	2	0	0	2
50	31	0	55	160	21.5	1	1	0	0	1
51	36	1	71	162	27.1	2	1	0	1	2
52	18	0	67	173	22.4	3	1	0	0	2
53	56	1	66	153	28.2	2	2	0	0	2
54	32	1	85	155	35.4	1	2	0	0	2
55	32	1	72	150	32	1	1	0	0	2
56	43	0	40	153	17	3	1	0	0	2
57	36	0	64	163	24	1	1	0	0	1
58	27	0	54	165	19.8	2	1	0	1	2
59	56	1	60	154	25.3	2	2	0	0	2
60	40	0	65	169	22.8	2	1	0	0	2

61	70	0	60	170	20.8	2	2	0	0	1
62	63	0	75	177	23.9	2	1	0	0	1
63	64	0	64	170	22.1	2	1	0	1	1
64	29	1	46	155	19.1	2	1	0	0	2
65	31	0	58	160	22.7	1	1	0	0	1
66	68	1	60	155	25	2	2	0	1	1
67	21	0	59	177	18.8	4	1	0	0	2
68	19	1	45	158	18	1	1	0	0	2
69	50	0	71	176	22.9	2	1	0	0	2
70	52	0	68	165	25	7	1	0	0	2
72	50	1	55	145	26.2	5	2	0	0	2
73	23	0	59	170	20.4	5	1	0	0	2
74	37	0	70	170	24.2	2	1	0	0	2
76	67	1	66	163	24.8	4	2	0	0	1
77	57	0	47	167	16.9	2	2	0	0	2
78	55	0	51	159	20.2	2	1	0	0	2
79	19	0	53	171	18.1	3	1	0	0	2
81	19	0	49	174	16.7	4	1	0	0	2
82	41	1	78	157	31.6	2	1	2	1	1
83	38	0	64	165	23.5	4	1	0	0	2
84	25	1	56	160	21.9	3	1	0	0	2
85	46	0	80	175	26.1	2	1	0	0	2
86	18	0	54	173	18	7	1	0	0	1
87	47	0	71	176	22.9	4	1	0	0	2
88	39	1	65	150	28.8	7	1	0	0	2
89	42	1	70	165	25.7	1	1	0	0	1
90	28	0	67	162	22.6	2	1	0	0	2
91	53	0	70	175	22.9	2	1	0	1	2
92	62	1	75	152	32.5	2	1	0	1	1
93	36	0	67	170	23.2	1	1	0	0	1
94	29	0	80	174	26.1	1	2	0	0	2

95	72	0	57	155	23.7	5	2	0	0	2
96	31	0	54	169	18.9	4	1	0	0	1
97	58	0	54	159	21.3	1	2	0	0	2
98	19	0	46	169	16.1	1	1	0	1	2
99	42	0	72	167	25.8	3	1	0	0	2
100	29	0	85	170	22.5	3	1	0	0	2
101	51	0	46	159	18.2	2	1	0	0	2
103	61	1	62	153	26.3	4	1	0	0	2
104	18	0	51	158	21	3	1	0	0	1
105	46	0	63	170	21.8	4	2	0	0	2
106	58	0	51	155	21.2	1	2	0	0	2
107	19	0	47	165	17.3	1	1	0	0	2
108	33	0	65	159	25.3	2	1	2	0	2
109	52	0	67	180	20.6	2	2	0	0	2
110	45	0	63	160	24.6	2	1	0	1	2
111	53	1	83	155	34.5	2	1	1	1	2
112	41	0	50	158	20.4	2	1	0	0	1
113	34	1	70	165	25.7	2	1	0	1	1
114	39	1	58	160	22.8	1	1	0	0	1
115	39	0	76	167	23.1	2	1	0	0	2
116	24	0	74	176	24.2	3	1	0	0	1
117	23	0	87	181	26.6	1	1	0	0	1
118	31	0	71	179	22.2	1	1	0	0	2
119	51	0	93	185	27.2	4	1	0	0	2
120	19	0	65	171	22.2	2	1	0	1	1
121	58	0	60	164	22.3	2	1	0	0	2
122	25	0	91	174	30	3	1	0	0	2
123	40	0	72	165	26.4	5	1	0	0	2
124	38	0	60	165	21.8	1	2	0	0	1
125	21	0	48	178	15.1	1	1	0	0	1
126	22	0	70	179	21.8	3	1	0	0	2

127	30	0	60	171	20.5	7	1	0	0	2
128	47	0	55	160	21.8	4	1	0	0	2
129	41	0	43	152	15.6	1	1	0	0	1
130	63	0	65	170	21	1	1	0	0	1
131	34	0	80	166	29	4	1	0	0	3
132	52	1	53	149	23.9	3	1	0	1	1
133	57	0	61	164	22.7	4	1	0	0	1
135	51	1	67	154	28.3	1	2	0	1	1
136	49	1	55	164	20.4	1	1	0	0	2
137	31	0	44	165	16.3	3	1	0	0	2
138	24	1	57	153	23	3	1	0	0	2
139	74	1	65	158	24	3	1	0	0	1
140	50	1	60	160	23.4	4	2	0	0	1
141	45	1	80	156	32.9	1	2	0	0	1
142	24	0	58	166	21	1	1	0	0	1
143	36	0	76	162	29	4	1	0	0	2
144	40	0	66	172	22.3	4	1	1	0	2
145	48	0	65	165	23.9	4	1	0	0	2
146	36	1	50	145	26.5	2	1	0	0	3
147	19	0	80	176	23	3	1	0	0	2
148	37	1	75	159	30	2	1	0	0	2
149	22	0	45	173	15	1	1	0	0	2
150	35	0	70	161	27	2	2	0	0	2
151	45	1	64	147	29.6	1	1	1	0	1
152	43	0	72	161	27.8	1	1	0	0	1
153	40	0	64	170	22	1	1	0	0	1
154	50	0	65	165	23.9	1	1	0	0	1
155	54	1	62	159	24.8	1	2	1	0	1
156	40	1	63	161	24.3	3	1	0	0	2
157	35	1	60	155	25	4	1	0	0	1
158	55	1	64	160	25	1	3	0	1	1

159	29	0	68	165	25	1	1	0	1	1
160	25	0	64	161	24.7	3	1	0	1	2
161	35	0				5	1	0	0	2
162	20	0	70	171	23.9	1	1	0	0	2
163	43	0	54	170	18.7	4	3	0	0	3
164	48	0	78	168	27.6	2	1	0	0	2
165	55	1	63	155	26.2	2	2	2	0	2
166	33	0	65	164	24.2	4	2	0	0	1
167	45	1	38	144	18.3	4	1	0	0	2
168	61	0	75	171	25.6	4	1	0	0	1
169	27	1	41	158	16.4	2	1	0	0	2
170	27	0	46	151	20.2	3	2	0	0	2
171	53	0	63	164	23.4	1	2	0	1	1
172	18	1	34	159	13.4	1	1	1	1	1
173	18	0	46	166	16.7	1	1	0	0	1
174	38	1	45	155	22.9	7	1	0	0	1
175	38	0	58	167	20.8	4	1	0	0	2
176	35	1	54	158	21.6	1	1	1	0	1
177	55	0	76	166	24.9	1	1	0	1	1
178	49	0	55	165	20.2	2	1	0	1	2
180	40	0	60	160	23.4	7	1	0	0	2
181	99	0	40	148	18.5	7	1	0	0	2
182	74	0	70	166	25.4	5	2	0	1	2
183	34	0	72	171	24.6	1	1	0	0	2
185	29	1	48	167	17.2	4	1	0	0	2
186	58	0	70	167	24.1	2	1	0	0	1
187	38	1	80	162	36.5	7	1	0	0	1
188	30	0				5	1	0	0	2
189	23	0	69	173	23.1	7	1	0	0	2
190	30	1	81	155	33.3	2	1	0	0	1
192	48	0	70	175	22.9	1	1	0	0	1

193	39	1	50	155	20.8	1	1	0	1	2
194	30	0	44	167	17	2	1	0	1	2
195	42	0	66	166	24	5	1	0	0	2
196	57	0	85	174	28.1	3	1	0	1	2